

# NMR Chemical Shifts in MNDO Approximation: Parameters and Results for H, C, N, and O

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**ABSTRACT:** The evaluation of the NMR chemical shift tensor has been implemented at the semiempirical MNDO level (modified neglect of diatomic overlap) for an *spd* basis using gauge-including atomic orbitals and analytic derivative theory. All relevant contributions to the chemical shifts of nuclei and points in space (nuclear independent chemical shifts, NICS), including three-center terms, can be computed. The execution time is dominated by the evaluation of the three-center terms, which typically require more than 90% of the total effort. Calculations with standard MNDO parameters overestimate the variation of the paramagnetic contributions, leading to an unsatisfactory description of the trends in chemical shifts. Agreement with experiment is improved by reoptimizing the electronic structure parameters to reproduce the experimental chemical shifts for 97 small molecules and ions. One-center energies, orbital exponents, and resonance  $\beta$  parameters of H, C, N, and O have been adjusted, for a total of 16 parameters. The reference set covers chemical shift ranges of 31, 346, 933, and 1650 parts per million (ppm) for H, C, N, and O, respectively. The final RMS deviations from experiment are 0.64, 13.6, 39.6, and 80.6 ppm for H, C, N, and O, respectively, down from 1.93, 36.8, 120.0, and 119.0 ppm for the original MNDO parameters. This corresponds to less than 5% of the total chemical shift range for each element. A significant fraction of the total error is due to small molecules with unusual bonding. On a larger set of solution NMR data for 384 common organic molecules, the RMS errors are reduced to 11.9, 38.8, and 61.7 ppm for C, N, and O, respectively. Three-center terms typically contribute a few ppm to the total chemical shift for all four elements studied, but they are essential for a qualitatively correct description of  $^1\text{H}$  chemical shifts and NICS. These terms are less important for C, N, and O,

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and can usually be omitted for these elements without significantly degrading the results. The overall quality of the results obtained with the NMR-specific parameterization is competitive with *ab initio* Hartree–Fock calculations. The relatively low computational cost permits studies of NMR chemical shifts and their trends in large molecules. Possible directions for future semiempirical NMR developments are outlined based on an analysis of some shortcomings of the present approach. © 1999 John Wiley & Sons, Inc. J Comput Chem 20: 1220–1245, 1999

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## Introduction

NMR chemical shifts are an important source of information on molecular structure and reactivity in many fields of chemistry.<sup>1–4</sup> They can be measured with high accuracy and sensitivity for increasingly complex systems, including large biomolecules, whose solution structures can be determined from NMR chemical shifts and coupling constants. NMR shieldings are a sensitive probe of the electronic structure, and they exhibit an intricate dependence on intramolecular and intermolecular interactions. The accurate theoretical calculation of absolute NMR shieldings is a challenging task that is best addressed by high-level *ab initio* methods. Approximate theoretical methods may be sufficient to study NMR chemical shifts, especially their trends for related molecules and their variations due to structural and environmental factors (e.g., conformations, substitutions, and solvent effects). Such approximate methods would be of great practical value, particularly for large molecules, if they can reproduce qualitative changes in the NMR chemical shifts reliably (without aiming for quantitative accuracy in the absolute shieldings).

Many *ab initio* and density functional approaches to the evaluation of the NMR chemical shifts have become available in recent years, facilitated by advances in analytic derivative theory.<sup>5</sup> Most of these approaches are based on the GIAO (gauge-including atomic orbitals)<sup>6,7</sup> and IGLO (individual gauge for localized orbitals)<sup>8,9</sup> concepts. There are implementations at the *ab initio* Hartree–Fock level (GIAO,<sup>6,7,10–13</sup> IGLO,<sup>8,9</sup> LORG<sup>14</sup>), at correlated *ab initio* levels [MP2-GIAO,<sup>15,16</sup> MP3-GIAO,<sup>17</sup> CCSD-GIAO,<sup>18</sup> CCSD(T)-GIAO,<sup>19</sup> CC2-GIAO,<sup>20</sup> SOLO,<sup>14</sup> MC-IGLO<sup>21,22</sup>], and within

density functional theory (DFT).<sup>13,23–28</sup> Several recent reviews of NMR shielding calculations are also available.<sup>29–31</sup> For small molecules, high-level *ab initio* calculations are approaching the experimental accuracy of the isotropic shift measurements, so that accounting for vibrational averaging and solvent effects becomes important when comparing experimental and theoretical results.<sup>18,19,32,33</sup> Lower-level *ab initio* and DFT calculations can currently handle molecules with up to about 100 atoms with an accuracy that is comparable to the experimental resolution for the chemical shift tensor components.<sup>13,34–37</sup>

Despite these tremendous recent advances, *ab initio* and DFT calculations of NMR chemical shifts remain relatively expensive, especially because large basis sets are generally required to approach convergence.<sup>9,13,18,19,36,37</sup> A reliable and less costly semiempirical method would clearly be useful for the treatment of larger systems and the rapid estimation of chemical shifts in cases where the full versatility of *ab initio* and DFT methods is not needed. A suitable semiempirical parameterization may also partly account for electron correlation and vibrational averaging effects, which are difficult to evaluate at the *ab initio* level.<sup>32,33</sup>

The early semiempirical literature on NMR chemical shifts reports several CNDO,<sup>38,39</sup> INDO,<sup>40–48</sup> and EHT<sup>49</sup> implementations. Lack of computational resources and reliable experimental data prevented an extensive parameterization of these early methods, and the accuracy of the results was generally not satisfactory. This may have contributed to the perception that semiempirical approaches cannot provide a semiquantitative description of the NMR parameters and, consequently, there has not been much activity in this field recently. Notable exceptions are the finite perturbation (FPT) MNDO/GIAO approach,<sup>50–52</sup> two special-purpose sum-over-states (SOS) MNDO

implementations,<sup>53,54</sup> gauge-dependent LORG-INDO/S,<sup>55</sup> and the commercial TNDO/2 method.<sup>56,57</sup> Only FPT-MNDO/GIAO and TNDO/2 have been designed as general purpose methods and therefore merit some comments in the present context.

The FPT-MNDO/GIAO approach includes all one-, two-, and three-center contributions to the chemical shifts. It has been parameterized for the NMR chemical shifts of C, N, O, and F by adjusting the resonance parameters  $\beta$  on H, C, N, O, and F. Using these parameters in our MNDO/GIAO implementation (see later), we find that FPT-MNDO/GIAO does not improve the correlation between experimental and theoretical chemical shifts compared with the standard MNDO parameters.<sup>58</sup> In addition, we can reproduce the reported FPT-MNDO/GIAO chemical shifts<sup>50,52</sup> only for carbon, but not for the other elements.

The TNDO/2 method appears to be extensively parameterized,<sup>57</sup> and some promising early results have been reported,<sup>59</sup> but a systematic assessment of the TNDO/2 results is not yet available. Moreover, the method has not yet been defined in the open literature, and the TNDO/2 parameters remain unpublished, so that an independent implementation is impossible.

The apparent lack of a reliable general purpose semiempirical method for the evaluation of NMR chemical shifts has motivated us to develop such a method on the basis of the MNDO<sup>60</sup> and MNDO/d<sup>61-65</sup> models. This article reports our implementation of NMR chemical shifts in the MNDO/d framework using gauge-including atomic orbitals and analytic derivative theory, and presents initial<sup>58</sup> and final NMR-specific semiempirical parameters for H, C, N, and O. The second section of this work outlines the theory of NMR chemical shifts of closed-shell molecules in MNDO approximation. The third section describes the key points of our implementation for MNDO and MNDO/d. The fourth section addresses the parameterization of the method, whereas the fifth section discusses some of the results. Conclusions and possible directions for future work are given in the last section.

## Theory

Detailed derivations of the analytic restricted Hartree-Fock (RHF) GIAO expressions for the chemical shift tensor components are available in

the literature.<sup>7,12,66</sup> We therefore provide only the expressions necessary to establish notation and concentrate on the consequences of the MNDO approximation.

The NMR shielding tensor components  $\sigma_{ab}$  are second-order properties given by the mixed derivative of the energy with respect to the components of the nuclear magnetic moment  $\vec{\mu}$  and the magnetic field strength  $\vec{B}$ :

$$\sigma_{ab} = \left. \frac{\partial^2 E}{\partial B_a \partial \mu_b} \right|_{\vec{\mu}, \vec{B}=0} \quad (1)$$

The absolute isotropic shielding  $\sigma$  is defined as:

$$\sigma = \frac{1}{3}(\sigma_{11} + \sigma_{22} + \sigma_{33}) \quad (2)$$

The NMR chemical shift is measured with respect to a reference compound:

$$\delta = \sigma_{\text{ref}} - \sigma \quad (3)$$

For the evaluation of the shielding tensor it is sufficient to include only the terms linear and bilinear in  $\vec{\mu}$  and  $\vec{B}$  in the one-electron Hamiltonian, which is then given by (atomic units)<sup>7,12,66</sup>:

$$\hat{h} = \hat{h}^{00} + i \sum_a \hat{h}^{a0} B_a + i \sum_b \hat{h}^{0b} \mu_b + \sum_{a,b} \hat{h}^{ab} B_a \mu_b \quad (4)$$

$$\hat{h}^{00} = -\frac{1}{2} \Delta + \sum_A \frac{Z_A}{|\vec{r} - \vec{R}_A|} \quad (5)$$

$$\hat{h}^{a0} = -\frac{1}{2c} \hat{L}_a^0 \quad (6)$$

$$\hat{h}^{0b} = -\frac{1}{c} \frac{\hat{L}_b^R}{|\vec{r} - \vec{R}|^3} \quad (7)$$

$$\hat{h}^{ab} = \frac{1}{2c^2} \frac{\delta_{ab} \vec{r} \cdot (\vec{r} - \vec{R}) - r_b (r_a - R_a)}{|\vec{r} - \vec{R}|^3} \quad (8)$$

where  $\vec{R}$  denotes the Cartesian coordinates of the magnetic nucleus. In eqs. (6) and (7), the imaginary unit  $i$  has been moved outside of the orbital momentum operator, so that the operators:

$$\hat{L}^0 = \vec{r} \times \vec{\nabla}, \quad \hat{L}^R = (\vec{r} - \vec{R}) \times \vec{\nabla} \quad (9)$$

and the operators  $\hat{h}^{00} - \hat{h}^{ab}$  in eqs. (4)–(8) are real.

In the GIAO approach, the origin independence of the chemical shift is ensured by introducing a field-dependent factor into the basis functions<sup>67</sup>:

$$\varphi(\vec{r} - \vec{R}) = \chi(\vec{r} - \vec{R}) \exp\left(-\frac{i}{2c} (\vec{B} \times \vec{R}) \cdot \vec{r}\right) \quad (10)$$

where  $\chi(\vec{r} - \vec{R})$  is a field-independent basis function centered at  $\vec{R}$ .

GIAO basis functions do not depend on the nuclear magnetic moment, so that differentiation with respect to  $\vec{\mu}$  may be performed using the Hellmann–Feynman theorem.<sup>5</sup> Subsequent differentiation with respect to  $\vec{B}$  introduces terms due to the derivatives of the Hamiltonian, the GIAOs, and the wave function. In the density matrix formulation, the resulting expression is given by<sup>12</sup>:

$$\sigma_{ab} = \sum_{\mu\nu} P_{\mu\nu} H_{\mu\nu}^{ab} - \sum_{\mu\nu} P_{\mu\nu}^a H_{\mu\nu}^{0b} \quad (11)$$

The purely real matrix elements  $H_{\mu\nu}^{ab}$  and  $H_{\mu\nu}^{0b}$  are:

$$H_{\mu\nu}^{ab} = \frac{\partial}{\partial B_a} \langle \varphi_\mu | \frac{\partial \hat{h}}{\partial \mu_b} | \varphi_\nu \rangle |_{\vec{\mu}, \vec{B}=0} \quad (12)$$

$$H_{\mu\nu}^{0b} = \langle \chi_\mu | \frac{\partial \hat{h}}{\partial i\mu_b} | \chi_\nu \rangle |_{\vec{\mu}, \vec{B}=0} \quad (13)$$

The imaginary part of the first-order density matrix,  $P^a$ , is formally defined as derivative of the zero-order density matrix  $P$  (elements  $P_{\mu\nu}^a$  and  $P_{\mu\nu}$ , respectively):

$$P_{\mu\nu}^a = \frac{\partial P_{\mu\nu}}{\partial iB_a} \quad (14)$$

The perturbed density matrix is obtained by solving the CPHF (coupled perturbed Hartree–Fock) equations, which take a particularly simple form in the MNDO approximation<sup>12,58</sup>:

$$F^a P + P F^a = P^a F + P F^a \quad (15)$$

$$P^a P + P P^a = 2 P^a \quad (16)$$

$$F^a = H^a + G(P^a) \quad (17)$$

$H^a$  is the imaginary part of the static derivative of the one-electron Hamiltonian with respect to the magnetic field:

$$\begin{aligned} H_{\mu\nu}^a &= \frac{\partial}{\partial iB_a} \langle \varphi_\mu | \hat{h} | \varphi_\nu \rangle |_{\vec{\mu}, \vec{B}=0} \\ &= \langle \chi_\mu | \hat{h}^{a0} - \frac{1}{2c} (\vec{r} \times \vec{R}_\mu)_a \hat{h}^{00} \\ &\quad + \frac{1}{2c} \hat{h}^{00} (\vec{r} \times \vec{R}_\nu)_a | \chi_\nu \rangle \end{aligned} \quad (18)$$

$G(P^a)$  is the analogue of the two-electron part of the Fock matrix built using the first-order density matrix in place of the unperturbed density.<sup>12</sup> The MNDO expression for  $G(P^a)$  is given elsewhere.<sup>58</sup>

Eq. (17) is considerably simpler than its *ab initio* analogue,<sup>12</sup> due to the cancellation of the field-dependent factors in all two-electron integrals that are retained in MNDO approximation. The CPHF equations [eqs. (15)–(17)] can be solved directly in the AO (atomic orbital) basis<sup>12</sup> or transformed into the explicitly linear nonredundant form.<sup>5,58,68</sup> In either case, the equations are solved by a rapidly converging iterative procedure.

In *ab initio* approaches, the matrix elements  $H_{\mu\nu}^a$  in eq. (18) are evaluated analytically. MNDO-type methods assume the two-center matrix elements  $H_{\mu\nu}^a$  of the operator  $\hat{h}^{00}$  to be proportional to the corresponding overlap integral  $S_{\mu\nu}$ :

$$H_{\mu\nu}^a = \langle \chi_\mu | \hat{h}^{00} | \chi_\nu \rangle \approx \beta_{\mu\nu} S_{\mu\nu} = H_{\mu\nu}^{\text{MNDO}} \quad (19)$$

Given this choice, a consistent approximation is required in eq. (18) to preserve the origin independence of the results. A local approximation in the spirit of eq. (19) is given by:

$$\chi_\mu^* \hat{h}^{00} \chi_\nu \approx \beta_{\mu\nu} \chi_\mu^* \chi_\nu \quad (20)$$

Applying eq. (20) to the matrix elements of the operator  $\vec{r} \hat{h}^{00}$  and explicitly separating the origin-dependent part, we obtain:

$$\langle \chi_\mu | \vec{r} \hat{h}^{00} | \chi_\nu \rangle \approx \vec{R}_\nu H_{\mu\nu}^{\text{MNDO}} + \beta_{\mu\nu} \langle \chi_\mu | \vec{r} - \vec{R}_\nu | \chi_\nu \rangle \quad (21)$$

Substitution of eq. (21) into eq. (18) results in a non-Hermitian expression.<sup>44,51</sup> Taking the anti-symmetric part, we arrive at the final semiempirical expression for  $H_{\mu\nu}^a$ :

$$\begin{aligned} H_{\mu\nu}^a(\text{MNDO}) &= \frac{1}{2c} \left\{ (\vec{R}_\mu \times \vec{R}_\nu) H_{\mu\nu}^{\text{MNDO}} + (\vec{R}_\mu - \vec{R}_\nu) \right. \\ &\quad \times (\beta_{\mu\nu} \langle \chi_\mu | \vec{r} - \vec{R}_\nu | \chi_\nu \rangle) \\ &\quad \left. - \frac{1}{2} \langle \chi_\mu | \hat{L}^{R_\nu} | \chi_\nu \rangle + \frac{1}{2} \langle \chi_\nu | \hat{L}^{R_\mu} | \chi_\mu \rangle \right\}_a \end{aligned} \quad (22)$$

Any origin dependence of  $H_{\mu\nu}^a(\text{MNDO})$  can only arise from the term containing the zero-order Hamiltonian matrix elements (the London<sup>67</sup> term). An arbitrary semiempirical expression for  $H_{\mu\nu}^{\text{MNDO}}$  in eq. (22) will lead to origin-independent chemical shifts as long as the same approximation is used to obtain the SCF wave function.<sup>66</sup>

An expression equivalent to eq. (22) was used in earlier INDO<sup>44</sup> and MNDO<sup>51</sup> models. Several INDO studies employed either the London term alone,<sup>40, 46</sup> or supplemented it with the orbital momentum term.<sup>48</sup> The use of the full expression [eq. (22)] was shown to be crucial for a qualitatively correct description of shielding in linear molecules.<sup>44</sup>

For analysis of the chemical shifts it is desirable to separate the chemical shift tensor into diamagnetic and paramagnetic contributions. The natural choice<sup>7</sup> is to designate all terms due to the unperturbed density as diamagnetic, and the terms containing the first-order density as paramagnetic. Unfortunately, this choice is not gauge-independent. To avoid this problem, we follow ref. 48 and

introduce gauge-independent expressions that seem to reflect the physical properties usually associated with diamagnetic and paramagnetic terms<sup>48</sup>:

$$\sigma_{ab} = \sigma_{ab}^{(d)} + \sigma_{ab}^{(p)} \quad (23)$$

$$\sigma_{ab}^{(d)} = \sum_{\mu\nu} H_{\mu\nu}^{ab(d)} P_{\mu\nu} \quad (24)$$

$$\sigma_{ab}^{(p)} = \sum_{\mu\nu} H_{\mu\nu}^{ab(p)} P_{\mu\nu} - \sum_{\mu\nu} H_{\mu\nu}^{0b} P_{\mu\nu}^a \quad (25)$$

$$H_{\mu\nu}^{0b} = -\frac{1}{c} \langle \chi_\mu | \frac{\hat{L}_b^R}{|\vec{r} - \vec{R}|^3} | \chi_\nu \rangle \quad (26)$$

$$H_{\mu\nu}^{ab(p)} = -\frac{1}{2c} \left( \vec{R}_\mu \times \vec{R}_\nu \right)_a H_{\mu\nu}^{0b} \quad (27)$$

$$H_{\mu\nu}^{ab(d)} = \frac{1}{2c^2} \left\{ \langle \chi_\mu | \left( (\vec{r} - \vec{R}_\mu) (\vec{R}_\nu - \vec{R}_\mu) \right)_a \frac{\hat{L}_b^R}{|\vec{r} - \vec{R}|^3} | \chi_\nu \rangle \right. \\ \left. + \langle \chi_\mu | \frac{\delta_{ab} (\vec{r} - \vec{R}_\nu) \cdot (\vec{r} - \vec{R}) - (\vec{r} - \vec{R}_\nu)_b (\vec{r} - \vec{R})_a}{|\vec{r} - \vec{R}|^3} | \chi_\nu \rangle \right\} \quad (28)$$

This separation into diamagnetic and paramagnetic terms is not unique. Adding an arbitrary real symmetric matrix to the matrix elements of eq. (27) while subtracting the same matrix from eq. (28) will leave all chemical shifts unchanged.

In summary, the general expressions [eqs. (11)–(14)] can be rewritten in terms of eqs. (23)–(28), which completely define the NMR chemical shifts in MNDO approximation, with the first-order density matrix being determined from the CPHF equations (15)–(17) using the approximation of eq. (22) for  $H_{\mu\nu}^a$ . It should be stressed that semiempirical approximations only enter the right-hand side of the CPHF equations, and thus only influence the paramagnetic terms via the first-order density matrix. The present model does not explicitly account for the contributions of the core electrons to the chemical shift (due to the neglect of core electrons in MNDO-type methods), so that absolute NMR shieldings will not be reproduced. However, because core contributions to the absolute shieldings are constant to within a few ppm,<sup>9</sup> and largely cancel in eq. (3), this shortcoming is unlikely to impede the parameterization for NMR

chemical shifts, at least for first-row elements (with a 1s core).

## Implementation

The evaluation of the NMR shielding tensors at the MNDO/d level was implemented in the MNDO94 program.<sup>65</sup> The perturbed density matrix  $P^a$  [eq. (14)] is obtained by solving the CPHF equations analytically as described previously.<sup>58, 69</sup> Unlike in the *ab initio* calculations<sup>12</sup> and some previous semiempirical implementations,<sup>51</sup> the determination of the first-order density requires only a minor fraction of the overall computational effort.

The matrix elements  $H_{\mu\nu}^a$  [eq. (22)] on the right-hand side of the CPHF equations contain two-center dipole moment integrals and overlap integrals over Slater AOs. The dipole moment integrals (involving basis functions with the orbital quantum number  $L$ ) can be reduced to linear combinations of overlap integrals with  $l' = L \pm 1$ .<sup>70</sup>

These overlap integrals are computed as described in ref. 71.

The evaluation of the  $H^{ab}$  and  $H^{0b}$  matrix elements [eqs. (26)–(28)] requires a large number of two- and three-center integrals. It would have been attractive to reduce the computational effort by employing suitable semiempirical approximations for those integrals. Unfortunately, the existing integral approximations<sup>60,72</sup> are oriented toward electron repulsion integrals and may be inappropriate for the singular operators in eqs. (26)–(28).<sup>72</sup> In our opinion, it is extremely difficult to construct approximate expressions for the corresponding matrix elements that are sufficiently accurate and preserve the origin independence of the resulting chemical shifts. We have therefore decided to use analytic expressions for the integrals in eqs. (26)–(28), which automatically guarantees the desired properties.

Several approaches to the calculation of the two-center integrals in eqs. (26)–(28) over Slater AOs have been reported in the literature.<sup>44,73–76</sup> The established procedures usually require evaluation of different primitive integrals for different operators, whereas the corresponding reduction formulas may be cumbersome to derive even for an *sp* basis.<sup>44</sup> Because our program supports *d* orbitals, the number of required reduction formulas and elementary integrals would have been significantly larger than in earlier semiempirical implementations,<sup>44</sup> making this route unmanageable. We therefore decided to pursue a more general approach to the two-center integrals, even at a potentially increased computational cost.

All two-center integrals required for the evaluation of the chemical shift tensor may be computed from primitive integrals of the form<sup>58,70</sup>:

$$\langle \chi(\vec{r}) | \frac{1}{r^3} | \chi'(\vec{r} - \vec{R}) \rangle \quad (29)$$

where  $\chi$  and  $\chi'$  are unnormalized Slater orbitals, and  $\chi$  is allowed to have a zero orbital exponent. The expressions for the transformations from the primitive to the full two-center integrals were derived with the help of the computer algebra system MATHEMATICA,<sup>77</sup> and are given elsewhere.<sup>58</sup> The primitive integrals are computed using a modification of the algorithm of ref. 71, with the elementary one-dimensional integrals being evaluated by a rapidly converging double infinite summation.<sup>58</sup> This approach is mildly numerically unstable for very small orbital exponents of the first Slater AO in eq. (29), which prevents evalua-

tion of the integral [eq. (29)] to full machine accuracy in this case, but does not affect the calculated chemical shifts.

The three-center magnetic integrals can be reduced to primitive integrals using the same techniques as for the two-center integrals.<sup>58</sup> The operators entering the primitive three-center integrals, given by:

$$\langle \chi(\vec{r} - \vec{R}) | \frac{\vec{r}}{r^3} | \chi'(\vec{r} - \vec{R}') \rangle \quad (30)$$

$$\langle \chi(\vec{r} - \vec{R}) | \frac{\hat{L}^0}{r^3} | \chi'(\vec{r} - \vec{R}') \rangle \quad (31)$$

cannot be decomposed any further because the  $\vec{r}$  [eq. (30)] and  $\hat{L}^0$  [eq. (31)] operators ensure integrability of the singular  $r^{-3}$  factor.

Evaluation of the primitive three-center integrals is much less straightforward than for the corresponding two-center integrals. Several approaches have been described in the literature, including Gaussian transforms,<sup>78–80</sup> Gaussian expansions,<sup>81</sup> variants of the single center (Löwdin) expansion,<sup>76,82–89</sup> Fourier transforms,<sup>90,91</sup> multipole expansions,<sup>92</sup> the  $\Sigma$ -separation method,<sup>93</sup> and numerical integration in the Cartesian space.<sup>25</sup> Some of the analytic approaches to the evaluation of the three-center integrals over Slater-type orbitals (STOs) are summarized in ref. 94. Despite the large number of available techniques, there appears to be no consensus with regard to the best approach for three-center STO integrals.

We have chosen to evaluate the primitive three-center integrals [eqs. (30)–(31)] using a single-center (Löwdin) expansion in terms of incomplete  $\gamma$ -functions,<sup>58,83</sup> and in terms of modified Bessel functions.<sup>82</sup> Determination of the primitive three-center integrals to the accuracy sufficient for the chemical shift calculations ( $10^{-5}$  a.u.) requires up to 40 terms in the Löwdin series, even if nonlinear convergence acceleration<sup>95</sup> is used. The  $\gamma$ -function expression, as well as the related exponential<sup>83</sup> and “C-matrix”<sup>87</sup> expressions are numerically unstable at high expansion orders, because total loss of significance occurs at expansion orders above 20 even if double precision is used throughout. On the other hand, the Bessel function expression<sup>82</sup> is numerically stable enough to converge the integrals to the desired accuracy, but it is extremely expensive computationally and cannot be employed in a practical semiempirical method.

An alternative to the direct calculation of the integrals over STOs is an expansion in terms of

Gaussians.<sup>81</sup> We have implemented such an evaluation of the primitive three-center integrals using the STO-nG<sup>81</sup> expansions and standard techniques.<sup>96</sup> Comparisons with the absolute shieldings computed with the "exact" STO integrals indicate that STO-nG expansions provide a good approximation for the magnetic three-center integrals. Already for STO-4G, the differences are typically below 0.5 ppm. For STO-9G, most of the deviations from the "exact" results are below 0.1 ppm. Because fitting errors in the absolute shieldings are systematic, and to a large extent cancel for the corresponding chemical shifts, the STO-4G expansions appear to be sufficient for the evaluation of the NMR chemical shifts. They are therefore used by default for the evaluation of the three-center terms.

In general, the s, p, and d STOs, which form the valence basis set in MNDO-type methods, may have different orbital exponents. The standard STO-nG expansions,<sup>81</sup> on the other hand, are optimized for the case of shared exponents, and may thus not provide the best possible description of individual Slater orbitals close to the nucleus. We have reoptimized the STO-nG expansions ( $n = 1-9$ ), without the restriction of shared exponents, to obtain the optimal fit to the radial factor  $r^{N-L-1}\exp(-r)$  of any given Slater orbital. For small expansion orders, including  $n = 4$ , this results in a significant improvement of the agreement between STO and STO-nG magnetic integrals. The reoptimized STO-4G expansions for the first five rows of the Periodic Table are given in Table I. Other expansions are available from the authors on request.

Use of the STO-4G expansions for the three-center integrals typically results in a speedup of about two orders of magnitude, compared with the fastest of the single-center expansion methods. To improve the computational efficiency for large molecules, atom pair prescreening is employed to discard all three-center terms that contribute less than  $10^{-5}$  ppm to the components of the shielding tensor on any of the atoms. For systems with more than 100 atoms, this reduces computation times typically by a factor of between 2 and 10. Even so, the evaluation of the three-center terms still accounts for more than 90% of the overall execution time.

Atom pair prescreening lowers the formal scaling of the number of three-center integrals in a molecule with  $N$  atoms to  $O(N^2)$ , compared to  $O(N^3)$  in the absence of a cutoff. The formal scaling of the number of two-center integrals is also

**TABLE I.**  
**STO-4G Expansions for Radial Part of Slater AOs.<sup>a</sup>**

$N - L$	$d_i$	$c_i$
1	5.216 844 534	0.247 466 171
	0.954 618 276	0.317 363 686
	0.265 203 410	0.248 749 179
	0.088 018 628	0.059 529 451
2	11.615 255 509	-0.164 974 732
	2.000 243 111	-0.201 373 419
	0.160 728 069	0.322 444 330
	0.061 257 445	0.128 509 318
3	1.513 265 591	-0.269 422 037
	0.426 249 751	-0.545 119 209
	0.076 433 209	0.654 891 468
	0.037 605 451	0.183 680 635
4	0.324 221 283	-1.079 577 882
	0.166 321 718	-1.661 495 890
	0.050 810 975	2.137 862 740
	0.028 290 666	0.544 057 785
5	0.860 228 425	1.048 397 874
	0.118 905 020	-12.073 269 348
	0.034 460 762	10.032 225 085
	0.019 747 988	0.972 000 867

$$^a r^{N-L-1}e^{-r} \approx \sum_{i=1}^4 c_i \exp(-d_i r^2).$$

$O(N^2)$ . For very large molecules this should make the CPHF step, which formally scales as  $O(N^3)$ , the most time-consuming part of the calculation. In practice, however, the STO-4G evaluation of the three-center terms still dominates the execution time even for molecules with several hundred atoms.

## Parameterization

Calculations using standard MNDO parameters overestimate the variation of the paramagnetic contribution to the NMR chemical shifts,<sup>58</sup> which is due to the systematic underestimation of excitation energies in MNDO.<sup>60</sup> This failure cannot be rectified without modifying the MNDO parameters.<sup>58</sup> We have therefore carried out an exploratory parameterization for H, C, N, and O, where a total of nine orbital exponents and resonance parameters were adjusted to reproduce liquid-phase chemical shift reference data from 299 small organic and inorganic molecules.<sup>58</sup> The resulting "method A" (MA) parameters are listed in Table II. Chemical shifts computed with the MA parameters show a significant improvement over the original MNDO parameters. A particularly

**TABLE II.**  
**Comparison of Standard and Optimized MNDO Parameters.<sup>a</sup>**

Element	Parameter	MNDO <sup>b</sup>	MA <sup>c</sup>	MB <sup>d</sup>
H	$U_{ss}$ (eV)	-11.906 276	-11.906 276	-13.436 18
	$\zeta$ (a.u.)	1.331 967	1.178 27	1.389 09
	$\beta_s$ (eV)	-6.989 064	-15.209 28	-28.938 65
	$\sigma_{ref}$ (ppm)	51.717	51.918	50.064
	$\sigma_{ref}(\text{N—H})$ (ppm)	44.186	46.415	42.873
	$\sigma_{ref}(\text{O—H})$ (ppm)	41.438	46.287	37.897
C	$U_{ss}$ (eV)	-52.279 745	-52.279 745	-58.421 97
	$U_{pp}$ (eV)	-39.205 558	-39.205 558	-39.800 82
	$\zeta$ (a.u.)	1.787 537	1.654 45	1.953 07
	$\beta_s$ (eV)	-18.985 044	-18.541 81	-41.955 87
	$\beta_p$ (eV)	-7.934 122	-12.811 44	-30.407 19
	$\sigma_{ref}$ (ppm)	-111.14	52.11	69.53
N	$U_{ss}$ (eV)	-71.932 122	-71.932 122	-78.940 77
	$U_{pp}$ (eV)	-57.172 319	-57.172 319	-60.516 71
	$\zeta$ (a.u.)	2.255 614	2.026 58	2.445 04
	$\beta_s = \beta_p$ (eV)	-20.495 758	-23.531 55	-64.530 46
	$\sigma_{ref}$ (ppm)	-552.48	-241.04	-172.20
	$U_{ss}$ (eV)	-99.643 09	-99.643 09	-105.073 55
O	$U_{pp}$ (eV)	-77.797 472	-77.797 472	-84.314 85
	$\zeta$ (a.u.)	2.699 905	2.202 74	2.806 91
	$\beta_s = \beta_p$ (eV)	-32.688 082	-19.804 85	-65.209 40
	$\sigma_{ref}$ (ppm)	-426.00	75.97	281.57

<sup>a</sup> One-center energies  $U_{ss}$  and  $U_{pp}$ , orbital exponents  $\zeta$ , and resonance parameters  $\beta_s$  and  $\beta_p$  (see ref. 60); reference shift  $\sigma_{ref}$ , see eq. (3) and text. <sup>b</sup> Ref. 60. Dependent  $\sigma_{ref}$  parameters are computed for the small reference set. <sup>c</sup> Optimized parameters from ref. 58. Dependent  $\sigma_{ref}$  parameters recomputed using the small reference set. Values of dependent  $\rho$  and  $D$  parameters as in original MNDO.<sup>60</sup> <sup>d</sup> This work. Dependent  $\rho$  and  $D$  parameters recomputed as described in ref. 60.

good agreement with experiment is observed for <sup>13</sup>C shifts in hydrocarbons.<sup>58</sup>

However, the MA parameterization was limited in scope: The adjustment of the parameters modified only the resonance integrals, and the NMR chemical shifts were computed only from the one- and two-center contributions (to save computational effort). The lack of three-center terms during the MA parameter optimization results in a non-unit correlation slope between experimental and calculated <sup>1</sup>H chemical shifts.<sup>58</sup> In addition, the shielding in molecules with multiple bonds involving heteroatoms is not well described, and there are systematic errors in other compounds with heteroatoms.<sup>58</sup> The NICS values for small rings are also unsatisfactory for the MA parameters,<sup>97</sup> due to the use of rather diffuse orbital exponents. We have therefore decided to perform a second and more thorough parameterization using the experience gained previously. In this second attempt, more parameters are adjusted (see later), three-center terms are included in the computation of NMR chemical shifts, and particular care is de-

voted to the selection of reference data. Two experimental data sets have been employed in the second parameterization, which are described in what follows.

The "small" set contains 97 small molecules and ions, with 107, 93, 37, and 53 chemical shift values for <sup>1</sup>H, <sup>13</sup>C, N (<sup>14</sup>N and <sup>15</sup>N), and <sup>17</sup>O, respectively. Because the isotopic dependence of the nitrogen chemical shifts arises from rovibrational effects (not covered presently) and is typically on the order of only 1 ppm<sup>98</sup> (i.e., significantly below our expected errors for this element), <sup>14</sup>N and <sup>15</sup>N chemical shifts are used interchangeably. The ranges of chemical shifts covered by the small set are 31.3, 346, 993, and 1650 ppm for H, C, N, and O, respectively. Only gas-phase data are included for <sup>1</sup>H shifts, which are particularly sensitive to medium effects. If necessary, <sup>1</sup>H shifts measured with respect to tetramethylsilane have been corrected to 298 K using the temperature dependence coefficients from ref. 99, in order to account for the unusually large temperature dependence of <sup>1</sup>H shielding in tetramethylsilane. A



relatively large number (54) of  $^{13}\text{C}$  chemical shifts in the small set are taken from gas-phase measurements, but there are no gas-phase data for some chemically important classes of compounds (e.g., ions). For nitrogen and oxygen, only a handful of gas-phase values are available in the literature for molecules containing H, C, N, and O (10 for N, and only 4 for O). To have a balanced and representative set of reference data, it is therefore inevitable to include liquid-phase chemical shifts in the parameterization for carbon, and especially for nitrogen and oxygen. As a general rule, liquid-state reference data are preferentially taken from experiments under conditions that minimize association and solvent effects. Moreover, whenever possible, there has been an attempt to eliminate unreliable reference data by analyzing several sources for the experimental values. The small set with a total of 290 NMR chemical shifts (175 gas phase values) is specified in Table III. All calculations on molecules from the small set have been performed at the optimized B3LYP/6-311G\*\* geometries,<sup>100–104</sup> to minimize errors due to molecular geometry.

The “large” parameterization set is a superset of the reference set used in the MA parameterization.<sup>58</sup> It contains 384 molecules and ions, with 346, 848, 239, and 171 liquid phase chemical shifts for H, C, N, and O, respectively. The corresponding chemical shift ranges are 19.3, 350, 977, and 1700 ppm, respectively. Although any obvious discrepancies in the experimental data have been corrected, the emphasis of the large set is on diversity rather than robustness. A significant portion of the data in the large set is derived from standard references.<sup>9,98,105–109</sup> The complete specification of the large set is available from the authors on request. Calculations involving the large set employ optimized semiempirical geometries (MNDO,<sup>60</sup> AM1,<sup>110</sup> and PM3<sup>111</sup>). Because MNDO tends to yield an incorrect (perpendicular) orientation of unsaturated side chains in aromatic molecules, the corresponding dihedral angles were constrained to planarity or to the experimental values (where available) in such cases. AM1 and PM3 geometries were not constrained.

The actual parameterization was carried out using the small reference set which initially contained fewer molecules than listed in Table III. In the course of the parameterization, the large set was used to identify potential candidates for inclusion into the small set. After each round of parameter optimization using the small set, outliers in the large set were examined for a common chemi-

cal motif. A representative molecule was then included into the small set subject to examination of the experimental data for potential discrepancies, which finally led to the set defined in Table III.

Semiempirical parameters were optimized by minimizing the goal function  $G$ , given by:

$$G = \sum_{X=\text{H,C,N,O}} W^X \times \sqrt{\frac{1}{N^X} \sum_{i=1}^{N^X} (\delta_i^X + \sigma_i^X - \sigma_{\text{ref}}^X)^2} + P \quad (32)$$

$$P = \sum_{X=\text{H,C,N,O}} w^X \sum_{E_i^X \leq E_{\text{max}}} (E_i^X - e_i^X)^2 \quad (33)$$

$\delta_i^X$  and  $\sigma_i^X$  are experimental chemical shifts and calculated absolute shieldings, respectively. The reference shieldings,  $\sigma_{\text{ref}}^X$ , were selected such that they minimize the overall RMS deviations from experiment for each element,  $X$ . The weights,  $W^X$ , were chosen to be 20, 3, 1, and 0.6 ppm<sup>-1</sup> for H, C, N, and O, respectively. Inclusion of the penalty function,  $P$ , is essential for obtaining physically reasonable parameters when one-center energies or one-center two-electron parameters are optimized (cf. ref. 40). The penalty function ensures that the experimental ( $E_i^X$ ) and calculated ( $e_i^X$ ) energies of the atomic states remain close to each other up to the chosen cutoff ( $E_{\text{max}}$ , 18 eV). The experimental atomic state energies were taken from ref. 112. The weights ( $w^X$ ) of the penalty function were 0.01 eV<sup>-2</sup> for C, N, and O, and 0.125 eV<sup>-2</sup> for H.

The goal function,  $G$ , was optimized using a quasi-Newton–Raphson minimization scheme with BFGS update<sup>113</sup> and DIIS<sup>114</sup> convergence acceleration, using gradients obtained by numerical differentiation. The parameterization program was run in parallel on a workstation cluster with an aggregate peak performance of more than 10 GFlops. The execution time for a single step of the parameter optimization (assuming 16 optimized variables) was typically about 30 minutes.

In the course of the parameter optimization, two alternatives to the standard MNDO expression [eq. (19)] for the zero-order resonance integral were examined:

$$H_{\mu\nu}^{(2)} = \beta_{\mu\nu} \sqrt{R_{\mu\nu}} \exp(-(\alpha_\mu + \alpha_\nu) R_{\mu\nu}^2) \quad (34)$$

$$H_{\mu\nu}^{(3)} = \beta_{\mu\nu} S_{\mu\nu} (1 - |S_{\mu\nu}|) \quad (35)$$

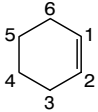
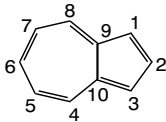
Eqs. (34)–(35) reflect consequences of basis set orthogonalization on  $H_{\mu\nu}$ .  $H_{\mu\nu}^{(2)}$  has been employed

**TABLE III.**  
**Results for Small Reference Set.**

Molecule	Atom	Exp. $\delta$ (ppm) <sup>a</sup>	Medium	MA3 $\delta$ (ppm)	MB3 $\delta$ (ppm)	Reference <sup>b</sup>
H <sup>+</sup>	H	30.61 <sup>c</sup>	gas	51.92	50.06	125
H <sup>-</sup>	H	6.37 <sup>c</sup>	gas	10.09	0.75	9,125
H <sub>2</sub>	H	4.22 <sup>c</sup>	gas	6.53	2.33	125, 126
HCN	H	2.83	gas	4.81	4.58	127
	C	113.00	gas	113.56	112.36	128
	N	-41.30	gas	-22.10	-6.15	129
NH <sub>3</sub>	N	-326.16	gas	-304.98	-326.32	129
H	H	-0.09 <sup>d</sup>	gas	-0.68	0.34	99, 130
H <sub>2</sub> O	O	0.00	gas	71.88	62.80	
	H	0.55 <sup>d</sup>	gas	0.31	1.20	99, 131
H <sub>2</sub> O <sub>2</sub>	O	210.00	H <sub>2</sub> O	258.20	412.69	132, 133
O <sub>3</sub>	O (terminal)	1634.00 <sup>c</sup>	unknown	2138.43	2091.43	133, 134
	O (middle)	1068.00 <sup>c</sup>	unknown	1255.54	1451.20	133, 134
CO <sub>2</sub>	C	136.35	gas	161.36	118.21	135
	O	100.60	gas	263.18	251.51	133, 136
CO	C	194.15	gas	313.35	235.03	135
	O	386.30	gas	349.55	418.00	133, 136
O=C=C=C=O	C(C=O)	136.70	CDCl <sub>3</sub>	141.91	126.41	128, 137
	C (middle)	-7.60	CDCl <sub>3</sub>	51.48	30.11	128, 137
N <sub>2</sub>	N	0.00	gas	16.41	26.14	
N=N=O	N (terminal)	-161.08	gas	-5.61	-56.61	129
	N (middle)	-72.89	gas	-116.61	-102.40	129
	O	141.50	gas	352.55	271.21	133, 136
ON—NO <sub>2</sub>	O (NO <sub>2</sub> )	461.00	neat	495.49	552.98	133, 138
	O (NO)	891.00	neat	703.79	819.04	133, 138
	N (NO <sub>2</sub> )	138.00	CH <sub>2</sub> Cl <sub>2</sub>	50.21	118.99	129, 139, 140
	N (NO)	366.00	CH <sub>2</sub> Cl <sub>2</sub>	310.35	332.71	129, 139, 140
N <sub>2</sub> O <sub>5</sub>	N	15.00	unknown	-22.59	-16.26	129, 141, 142
N <sub>2</sub> H <sub>4</sub>	N	-260.00	unknown	-244.34	-256.11	129, 140, 143
CH <sub>4</sub>	C	0.00	gas	1.15	5.74	
	H	0.00	gas	-0.15	0.70	
C <sub>2</sub> H <sub>6</sub>	C	14.22	gas	15.55	19.57	144
	H	0.74	gas	0.49	1.16	99
C <sub>3</sub> H <sub>8</sub>	C (—CH <sub>3</sub> )	24.15	gas	17.06	20.94	145
	C (—CH <sub>2</sub> —)	25.73	gas	29.05	32.85	145
	H (—CH <sub>3</sub> )	0.80	gas	0.57	1.23	145
	H (—CH <sub>2</sub> —)	1.25	gas	1.08	1.56	145
Cyclopropane	C	10.11	gas	26.47	22.90	144
	H	0.07	gas	1.08	1.09	99
<i>n</i> -Butane	C (—CH <sub>3</sub> )	21.30	gas	17.00	20.97	145
	C (—CH <sub>2</sub> —)	34.77	gas	30.24	33.77	145
	H (—CH <sub>3</sub> )	0.80	gas	0.62	1.32	145
	H (—CH <sub>2</sub> —)	1.23	gas	1.09	1.56	145
Isobutane	C (>CH—)	33.45	gas	41.48	45.42	145
	C (—CH <sub>3</sub> )	32.64	gas	18.73	22.36	145
	H (>CH—)	1.59	gas	1.64	1.93	145
	H (—CH <sub>3</sub> )	0.77	gas	0.62	1.27	145
Cyclobutane	C	30.57	gas	34.63	37.05	144
	H	1.90	gas	1.69	1.81	99
Cyclopentane	H	1.45	gas	1.39	1.78	99

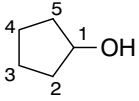
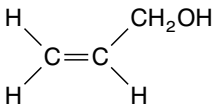
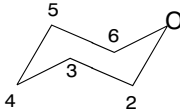
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**TABLE III.**  
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Molecule	Atom	Exp. $\delta$ (ppm) <sup>a</sup>	Medium	MA3 $\delta$ (ppm)	MB3 $\delta$ (ppm)	Reference <sup>b</sup>
<i>n</i> -Pentane	C (1)	21.59	gas	17.09	21.03	144
	C (2)	32.06	gas	30.27	33.93	144
	C (3)	44.44	gas	31.61	34.87	144
Isopentane	C (1, 2')	30.11	gas	18.55	22.28	145
	C (2)	40.19	gas	42.77	46.67	145
	C (3)	41.67	gas	31.76	35.24	145
	C (4)	19.38	gas	16.65	20.59	145
Neopentane	C (> C <)	36.79	gas	53.79	58.47	145
	C (—CH <sub>3</sub> )	39.66	gas	20.71	24.08	145
	H	0.82	gas	0.67	1.29	99
Cyclohexane	H (axial)	1.62	gas	1.11	1.58	146, 147
	H (equatorial)	1.18	gas	1.19	1.76	146, 147
C(C <sub>2</sub> H <sub>5</sub> ) <sub>4</sub>	H (—CH <sub>2</sub> —)	1.27	gas	1.12	1.64	148
	H (—CH <sub>3</sub> )	0.72	gas	0.65	1.36	148
C(CH <sub>3</sub> ) <sub>3</sub> <sup>+</sup>	C (> C <sup>+</sup> —)	338.50	SO <sub>2</sub> ClF/SbF <sub>5</sub>	297.14	329.73	128, 149
	C (—CH <sub>3</sub> )	56.80	SO <sub>2</sub> /SbF <sub>5</sub>	41.04	36.87	128, 149
C <sub>2</sub> H <sub>4</sub>	C	130.46	gas	128.05	131.94	145
	H	5.18	gas	6.74	5.11	99
CH <sub>2</sub> =CHCH <sub>3</sub>	C (=CH <sub>2</sub> )	123.22	gas	121.88	126.88	150
	C (=CH—)	142.48	gas	134.25	140.07	150
	C (—CH <sub>3</sub> )	26.21	gas	21.38	24.30	150
(CH <sub>3</sub> ) <sub>2</sub> C=C(CH <sub>3</sub> ) <sub>2</sub>	C (> C=)	132.50	gas	131.10	139.08	135, 151
	C (—CH <sub>3</sub> )	33.10	gas	20.69	23.88	135, 151
	H	1.51	gas	1.25	1.80	146
	H (1, 2)	5.51 <sup>d</sup>	gas	6.93	5.51	99, 152
	H (3, 6)	1.89 <sup>d</sup>	gas	1.81	2.22	99, 152
	H (4, 5)	1.56 <sup>d</sup>	gas	1.31	1.73	99, 152
H <sub>2</sub> C=C=CH <sub>2</sub>	C (=CH <sub>2</sub> )	79.73	gas	93.55	100.67	144
	C (=C=)	224.29	gas	183.73	198.03	144
C <sub>2</sub> H <sub>2</sub>	C	77.90	gas	87.30	94.74	128
	H	1.33	gas	3.16	3.26	99
H <sub>3</sub> CCCCH <sub>3</sub>	H	1.46	gas	1.12	1.74	99
Benzene	C	137.23	gas	132.06	136.70	144
	H	7.09	gas	8.70	6.82	99, 153
Toluene	C (ipso)	147.68	gas	141.13	146.89	144
	C (ortho)	137.62	gas	130.87	135.79	144
	C (meta)	138.24	gas	132.50	136.94	144
	C (para)	134.76	gas	130.42	135.29	144
	C (—CH <sub>3</sub> )	28.72	gas	23.49	26.23	144
	C (2)	146.40	CS <sub>2</sub>	139.52	145.80	144, 154
	C (1, 3)	127.70	CS <sub>2</sub>	122.31	125.20	144, 154
	C (9, 10)	149.40	CS <sub>2</sub>	134.60	141.41	144, 154
	C (4, 8)	145.50	CS <sub>2</sub>	143.28	148.09	144, 154
	C (5, 7)	131.80	CS <sub>2</sub>	127.33	131.83	144, 154
	C (6)	146.00	CS <sub>2</sub>	143.64	148.61	144, 154
	C (ipso)	59.20	SO <sub>2</sub> ClF/SbF <sub>5</sub>	51.85	46.54	128, 155
	C (ortho)	193.60	SO <sub>2</sub> ClF/SbF <sub>5</sub>	187.93	199.60	128, 155
	C (meta)	143.90	SO <sub>2</sub> ClF/SbF <sub>5</sub>	132.17	135.10	128, 155
C <sub>6</sub> H <sub>7</sub> <sup>+</sup>	C (para)	185.10	SO <sub>2</sub> ClF/SbF <sub>5</sub>	179.21	190.31	128, 155

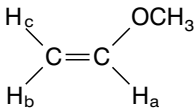
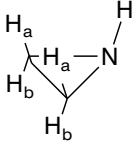
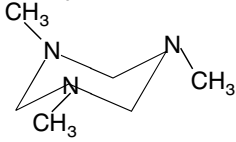
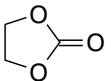
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TABLE III.  
(Continued)

Molecule	Atom	Exp. $\delta$ (ppm) <sup>a</sup>	Medium	MA3 $\delta$ (ppm)	MB3 $\delta$ (ppm)	Reference <sup>b</sup>
CH <sub>3</sub> OH	C	58.09	gas	58.51	69.44	144
	H (—CH <sub>3</sub> )	3.30 <sup>d</sup>	gas	2.32	2.67	99, 131
	H (—OH)	−0.09 <sup>d</sup>	gas	−0.10	0.14	99, 131
	O	−1.00	neat	69.63	53.47	133, 156
C <sub>2</sub> H <sub>5</sub> OH	C (—CH <sub>2</sub> —)	67.49	gas	69.34	80.71	144
	C (—CH <sub>3</sub> )	26.57	gas	16.26	19.08	144
	H (—CH <sub>2</sub> —)	3.53 <sup>d</sup>	gas	2.74	2.98	99, 131
	H (—CH <sub>3</sub> )	1.25 <sup>d</sup>	gas	0.83	1.41	99, 131
	H (—OH)	0.33 <sup>d</sup>	gas	−0.03	0.19	99, 131
	O	42.00	neat	80.40	60.48	133, 156
<i>n</i> -C <sub>3</sub> H <sub>7</sub> OH	H (1)	3.45 <sup>d</sup>	gas	2.87	3.00	99, 131
	H (2)	1.44 <sup>d</sup>	gas	1.24	1.88	99, 131
	H (3)	0.83 <sup>d</sup>	gas	0.55	1.28	99, 131
	H (—OH)	0.40 <sup>d</sup>	gas	0.24	0.43	99, 131
	O	36.00	neat	71.38	59.72	133, 156
iso-C <sub>3</sub> H <sub>7</sub> OH	H (—CH <sub>3</sub> )	1.01 <sup>d</sup>	gas	0.79	1.46	99, 131
	H (>CH—)	3.81 <sup>d</sup>	gas	3.37	3.32	99, 131
	H (—OH)	0.47 <sup>d</sup>	gas	0.12	0.31	99, 131
	O	76.00	neat	81.61	66.43	133, 156
tert-C <sub>4</sub> H <sub>9</sub> OH	H (—OH)	0.47 <sup>d</sup>	gas	0.16	0.30	99, 131
	H (—CH <sub>3</sub> )	1.08 <sup>d</sup>	gas	0.86	1.46	99, 131
	O	98.00	neat	90.77	72.79	133, 156
	H (1)	4.14 <sup>d</sup>	gas	3.62	3.47	99, 131
	H (2, 5)	1.66 <sup>d</sup>	gas	1.57	1.99	99, 131
	H (3, 4)	1.46 <sup>d</sup>	gas	1.48	1.86	99, 131
	H (—OH)	0.49 <sup>d</sup>	gas	0.49	0.60	99, 131
	O	67.00	neat	78.53	64.04	133, 156
HOCH <sub>2</sub> CH <sub>2</sub> OH	H (—OH)	1.03 <sup>d</sup>	gas	0.77	0.64	99, 131
	H (—CH <sub>2</sub> —)	3.50 <sup>d</sup>	gas	2.93	3.22	99, 131
	O	31.00	neat	68.03	56.39	133, 156
	H (—CH <sub>2</sub> —)	3.93 <sup>d</sup>	gas	3.52	3.45	99, 131
	H (=CH—)	5.87 <sup>d</sup>	gas	7.14	5.63	99, 131
	H (—OH)	0.46 <sup>d</sup>	gas	0.53	0.58	99, 131
	O	35.00	neat	76.38	60.91	133, 156
HOCH <sub>2</sub> CH <sub>2</sub> NH <sub>2</sub>	H (—CH <sub>2</sub> O—)	3.38 <sup>d</sup>	gas	2.64	3.05	99, 131
	H (—CH <sub>2</sub> N <)	2.67 <sup>d</sup>	gas	1.97	2.15	99, 131
	H (—OH)	1.29 <sup>d</sup>	gas	1.79	1.43	99, 131
C <sub>6</sub> H <sub>5</sub> OH	H (—OH)	3.65 <sup>d</sup>	gas	4.75	3.21	99, 131
	O	115.00	benzene	126.88	116.70	133, 157
(CH <sub>3</sub> ) <sub>2</sub> O	H	3.10	gas	2.36	2.46	148
	O	−6.00	CDCl <sub>3</sub>	73.58	44.49	133, 157
Ethylene oxide (C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> O	O	−13.00	neat	105.67	38.24	133, 157
	H (—CH <sub>2</sub> —)	3.29	gas	2.84	2.85	148
	H (—CH <sub>3</sub> )	1.02	gas	0.70	1.38	148
	O	52.00	neat	73.76	53.61	133, 157
	H (2, 6, eq)	3.18 <sup>d</sup>	gas	2.64	2.85	99, 158
	H (2, 6, ax)	3.74 <sup>d</sup>	gas	2.80	2.77	99, 158
	H (3, 5)	1.52 <sup>d</sup>	gas	1.36	1.75	99, 158
	H (4)	1.41 <sup>d</sup>	gas	1.26	1.65	99, 158
	O	46.00	CDCl <sub>3</sub>	83.14	50.36	133, 157

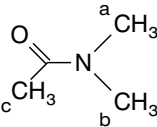
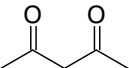
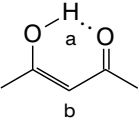
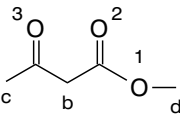
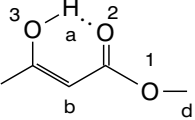
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**TABLE III.**  
(Continued)

Molecule	Atom	Exp. $\delta$ (ppm) <sup>a</sup>	Medium	MA3 $\delta$ (ppm)	MB3 $\delta$ (ppm)	Reference <sup>b</sup>
	H (a)	6.31	gas	6.72	4.71	99, 159
	H (b)	3.73	gas	5.64	4.36	99, 159
	H (c)	3.97	gas	5.58	4.44	99, 159
	H (—CH <sub>3</sub> )	3.34	gas	2.94	2.88	99, 159
	O	95.00	CCl <sub>4</sub>	116.78	101.12	133, 160
CH <sub>3</sub> NH <sub>2</sub>	C	36.80	gas	32.75	35.00	128
	N	−311.70	gas	−287.66	−315.10	129, 161
	H (—NH <sub>2</sub> )	0.27 <sup>d</sup>	gas	−0.39	0.23	99, 130
(CH <sub>3</sub> ) <sub>2</sub> NH	H (> NH)	0.06 <sup>d</sup>	gas	−0.15	0.09	99, 130
	N	−300.10	gas	−275.57	−307.27	129, 161
(CH <sub>3</sub> ) <sub>3</sub> N	N	−297.50	gas	−264.77	−299.96	129, 161
	H (—CH <sub>3</sub> )	2.03	gas	1.33	1.56	148
(C <sub>2</sub> H <sub>5</sub> ) <sub>3</sub> N	H (—CH <sub>2</sub> —)	2.39	gas	1.71	1.90	148
	H (—CH <sub>3</sub> )	0.90	gas	0.67	1.39	148
	N	−259.00	cyclohexane	−258.66	−293.55	129, 162
	H (> NH)	−0.71 <sup>d</sup>	gas	1.17	0.39	99, 163
	H (a)	1.42 <sup>d</sup>	gas	1.44	1.41	99, 163
	H (b)	1.17 <sup>d</sup>	gas	1.45	1.57	99, 163
	N	−326.00	neat	−246.12	−295.38	129, 140, 164
	H (> CH <sub>2</sub> , eq)	3.44 <sup>d</sup>	gas	2.09	2.00	99, 165
	H (> CH <sub>2</sub> , ax)	2.58 <sup>d</sup>	gas	2.28	1.94	99, 165
	H (—CH <sub>3</sub> )	2.11 <sup>d</sup>	gas	1.50	1.69	99, 165
	H (> CH <sub>2</sub> , eq)	3.44 <sup>d</sup>	gas	2.09	2.00	99, 165
	H (> CH <sub>2</sub> , ax)	2.58 <sup>d</sup>	gas	2.28	1.94	99, 165
C <sub>6</sub> H <sub>5</sub> NH <sub>2</sub>	H (—NH <sub>2</sub> )	3.07 <sup>d</sup>	gas	2.83	2.60	99, 130
	N	−248.00	DMSO	−265.06	−278.07	129, 140, 166
H <sub>2</sub> C=C=O	C (H <sub>2</sub> C=)	9.50	CDCl <sub>3</sub>	59.19	45.01	128, 167
	C (=CO)	201.00	CDCl <sub>3</sub>	190.28	180.84	128, 167
CH <sub>3</sub> CHO	C (—CHO)	201.72	gas	201.01	203.17	144
	C (—CH <sub>3</sub> )	38.01	gas	25.35	25.22	144
	H (—CH <sub>3</sub> )	1.79	gas	2.05	2.16	148
	O	628.00	neat	565.50	534.89	133, 168
	C	195.20	gas	206.04	199.99	128, 169, 170
H <sub>2</sub> C=O	C	171.38	gas	180.01	159.04	144
	O	290.00	neat	289.54	279.96	132, 133
	O (—O—)	309.00	CH <sub>3</sub> CN	188.93	197.90	133, 171
(CH <sub>3</sub> C(O)) <sub>2</sub> O	O (=O)	447.00	CH <sub>3</sub> CN	415.14	410.74	133, 171
	O (=O)	249.00	neat	345.97	327.91	133, 172
	O (—O—)	143.00	neat	163.96	132.56	133, 172
	O	290.00	neat	289.54	279.96	132, 133
	O (—O—)	309.00	CH <sub>3</sub> CN	188.93	197.90	133, 171
	O (=O)	447.00	CH <sub>3</sub> CN	415.14	410.74	133, 171
	O (=O)	249.00	neat	345.97	327.91	133, 172
	O (—O—)	143.00	neat	163.96	132.56	133, 172
	O	290.00	neat	289.54	279.96	132, 133
Acetone	C (> C=O)	208.20	gas	201.60	209.22	128
	C (—CH <sub>3</sub> )	37.10	gas	24.83	25.36	128
	H	1.79	gas	1.99	2.10	146
	O	623.60	neat	539.21	516.59	121, 133, 136
	H (HC(O)—)	8.00	gas	8.56	5.44	173
HC(O)NH <sub>2</sub>	H (—NH <sub>2</sub> )	4.37	gas	4.18	3.32	173
	O	370.00	acetone	380.54	355.92	133, 174
	N	−197.00	CH <sub>3</sub> CN	−248.22	−244.31	129, 175
	C	172.00	CH <sub>3</sub> CN	158.96	152.20	128, 175
	O	370.00	acetone	380.54	355.92	133, 174


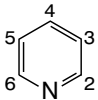
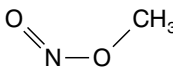
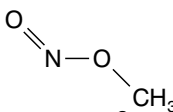
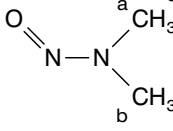
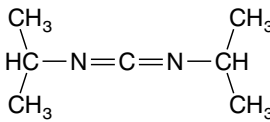
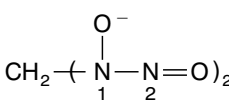
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TABLE III.  
(Continued)

Molecule	Atom	Exp. $\delta$ (ppm) <sup>a</sup>	Medium	MA3 $\delta$ (ppm)	MB3 $\delta$ (ppm)	Reference <sup>b</sup>
	H (c)	1.75 <sup>d</sup>	gas	1.35	1.60	99, 176
	H (a)	2.71 <sup>d</sup>	gas	2.39	2.39	99, 176
	H (b)	2.76 <sup>d</sup>	gas	2.06	2.11	99, 176
	O	375.00	acetone	379.50	349.09	133, 174
	N	−209.00	neat	−233.93	−233.06	129, 140, 177
	C	177.00	CDCl <sub>3</sub>	164.59	161.28	128, 177
	H (—CH <sub>3</sub> )	1.89 <sup>d</sup>	gas	2.18	2.27	99, 178
	H (>CH <sub>2</sub> )	3.18 <sup>d</sup>	gas	4.17	3.23	99, 178
	O	602.00	neat	536.31	516.14	133, 179
	H (—CH <sub>3</sub> )	1.74 <sup>d</sup>	gas	1.92	2.06	99, 178
	H (b)	5.17 <sup>d</sup>	gas	6.64	5.03	99, 178
	H (a)	15.10 <sup>c, d</sup>	gas	12.78	8.23	99, 178
	O	310.00	neat	275.65	278.50	133, 179
	H (c)	1.94 <sup>d</sup>	gas	2.39	2.27	99, 178
	H (d)	3.52 <sup>d</sup>	gas	3.43	3.32	99, 178
	H (b)	3.04 <sup>d</sup>	gas	3.59	2.77	99, 178
	O (3)	614.00	CHCl <sub>3</sub>	544.68	523.53	133, 180
	O (2)	401.00	CHCl <sub>3</sub>	407.47	384.18	133, 180
	O (1)	209.00	CHCl <sub>3</sub>	155.21	154.99	133, 180
	H (c)	1.70 <sup>d</sup>	gas	1.71	1.96	99, 178
	H (d)	3.52 <sup>d</sup>	gas	3.33	3.19	99, 178
	H (b)	4.75 <sup>d</sup>	gas	6.28	4.61	99, 178
	H (a)	11.85 <sup>c, d</sup>	gas	10.93	6.77	99, 178
	O (3)	160.00	CHCl <sub>3</sub>	138.34	154.60	133, 180
	O (2)	332.00	CHCl <sub>3</sub>	340.98	317.57	133, 180
	O (1)	209.00	CHCl <sub>3</sub>	148.81	142.59	133, 180
	C (>C=O)	194.00	CDCl <sub>3</sub>	191.07	182.85	128, 181
	C (=CH—)	143.40	CDCl <sub>3</sub>	129.19	141.00	128, 181
	O	671.00	toluene	631.02	544.60	133, 182
para-benzoquinone						
CH <sub>3</sub> CN	C (—CH <sub>3</sub> )	7.40	gas	16.81	19.28	128
	C (—CN)	121.30	gas	112.30	115.69	128
	N	−52.80	gas	−16.17	−4.28	129, 161
	H	1.53	gas	1.28	1.82	146
C <sub>2</sub> H <sub>5</sub> CN	H (—CH <sub>2</sub> —)	2.00	gas	1.77	2.19	148
	H (—CH <sub>3</sub> )	1.08	gas	0.78	1.30	148
	N	−64.00	unknown	−15.12	−3.14	129, 140, 183
CH <sub>3</sub> NC	N	−141.00	neat	−214.73	−173.38	129, 184
	C (—CH <sub>3</sub> )	33.80	CCl <sub>4</sub> /CD <sub>3</sub> CN	41.28	37.99	128, 185
	C (—NC)	165.20	CCl <sub>4</sub> /CD <sub>3</sub> CN	217.16	204.68	128, 185
C <sub>6</sub> H <sub>5</sub> OCN	N	−136.30	neat	−41.54	−70.43	118, 129
	C (—OCN)	116.20	neat	98.84	91.92	118, 128
	C (ipso)	160.50	neat	155.67	156.61	118, 128
	C (ortho)	122.80	neat	121.48	125.92	118, 128
	C (meta)	138.20	neat	134.74	139.63	118, 128
	C (para)	134.50	neat	131.01	135.82	118, 128
CH <sub>3</sub> NCO	C (—NCO)	128.30	neat	130.58	110.03	128, 186
	C (—CH <sub>3</sub> )	33.10	neat	42.13	40.21	128, 186
	O	119.70	CH <sub>3</sub> CN	228.05	228.79	133, 187
	N	−290.60	neat	−218.02	−234.17	129, 188

(Continued)

**TABLE III.**  
(Continued)

Molecule	Atom	Exp. $\delta$ (ppm) <sup>a</sup>	Medium	MA3 $\delta$ (ppm)	MB3 $\delta$ (ppm)	Reference <sup>b</sup>
$\text{CH}_2(\text{CN})_2$	N	-53.00	unknown	-10.39	3.95	129, 189
	C ( $-\text{CH}$ )	117.70	neat	107.21	110.51	128, 190
	C ( $> \text{CH}_2$ )	15.80	neat	29.61	31.36	128, 190
$\text{CH}(\text{CN})_2^-$	C ( $> \text{CH}^-$ )	4.90	unknown	53.80	36.37	128, 191
	C ( $-\text{CN}$ )	137.30	unknown	124.04	126.00	128, 191
	C (2, 5)	151.97	gas	159.95	153.30	144
	C (3, 4)	117.84	gas	118.10	122.21	144
	O	277.00	neat	241.80	243.49	132, 133
	C (2, 6)	160.17	gas	140.16	144.04	144
	C (3, 5)	132.07	gas	126.19	128.04	144
	C (4)	143.52	gas	136.43	146.37	144
	N	17.10	gas	14.37	-8.94	129, 192
$\text{CH}_3\text{NO}_2$	H	3.91	gas	3.74	2.80	148
	O	639.00	neat	590.50	588.86	133, 193
	N	74.70	neat	15.58	51.79	129
	H	3.36 <sup>d</sup>	gas	3.69	4.01	99, 194
	O ( $-\text{O}-$ )	456.00	neat	284.75	328.15	133, 138
	O ( $-\text{NO}$ )	826.00	neat	676.93	784.32	133, 138
	H	4.45 <sup>d</sup>	gas	3.81	3.29	99, 194
	O ( $-\text{O}-$ )	456.00	neat	343.13	341.53	133, 138
	O ( $-\text{NO}$ )	826.00	neat	758.52	810.60	133, 138
	H (a)	2.71 <sup>d</sup>	gas	2.66	2.64	99, 195
	H (b)	3.50 <sup>d</sup>	gas	3.09	3.14	99, 195
	O	696.00	neat	619.61	664.03	133, 138
	N ( $-\text{N} <$ )	-76.00	neat	-158.66	-120.50	129, 140, 196
	N ( $-\text{NO}$ )	227.00	neat	190.68	254.56	129, 140, 196
	C (a)	39.40	$\text{CDCl}_3$	39.02	40.12	128, 196
$(\text{C}_2\text{H}_5)_2\text{O}_2$	C (b)	47.20	$\text{CDCl}_3$	41.02	40.20	128, 196
	O	289.00	$\text{CDCl}_3$	280.47	446.35	133, 197
$\text{C}_6\text{H}_5\text{NO}$	N	607.20	cyclohexane	531.30	565.99	119, 129
	O	949.00 <sup>e</sup>	$\text{CH}_2\text{Cl}_2$	1256.72	1193.95	120, 133
$\text{C}_2\text{H}_5\text{ONO}_2$	N	38.00	neat	-8.74	-1.67	129, 142
	O ( $-\text{O}-$ )	376.00	neat	296.43	300.82	133, 198
	O ( $-\text{NO}_2$ )	506.00	neat	506.67	481.53	133, 198
$\text{H}_2\text{C}=\text{N}=\text{N}$	C	30.10	$\text{CDCl}_3$	81.96	53.18	128, 199
	N ( $=\text{N}=\text{N}$ )	-16.20	$\text{CD}_3\text{OD}$	-115.23	-63.97	129, 140, 200
	N ( $=\text{N}$ )	90.40	$\text{CD}_3\text{OD}$	98.64	88.78	129, 140, 200
	C ( $=\text{C}=\text{C}$ )	147.20	$\text{CDCl}_3$	120.82	113.72	128, 201
	C ( $-\text{CH} <$ )	56.00	$\text{CDCl}_3$	59.25	63.86	128, 201
	C ( $-\text{CH}_3$ )	31.80	$\text{CDCl}_3$	18.32	21.33	128, 201
	N	-196.90	cyclohexane	-181.45	-211.79	129, 202
$\text{CH}_3-\text{N}=\text{N}=\text{N}$ 1 2 3	N (1)	-245.10	benzene-d6	-132.42	-204.16	98, 129, 203
	N (2)	-53.60	benzene-d6	-128.72	-98.93	98, 129, 203
	N (3)	-94.80	benzene-d6	0.18	-50.14	98, 129, 203
	N (1)	-7.80	$\text{D}_2\text{O}$	-73.04	-52.70	129, 139, 140
	N (2)	137.20	$\text{D}_2\text{O}$	155.36	158.62	129, 139, 140

<sup>a</sup> NMR chemical shifts relative to gaseous reference compounds:  $\text{CH}_4$  for  $^{13}\text{C}$  and  $^1\text{H}$ ;  $\text{N}_2$  for  $^{14}\text{N}$  and  $^{15}\text{N}$ ;  $\text{H}_2\text{O}$  for  $^{17}\text{O}$ . <sup>b</sup> Normally the reference with the highest number indicates the source of the original chemical shift data. <sup>c</sup> Excluded from statistics (see text).

<sup>d</sup> Original measurement with respect to gaseous tetramethylsilane at elevated temperature. Converted to the methane scale using temperature dependence data from ref. 99. <sup>e</sup> Ref. 120 interchanges experimental values for  $^{15}\text{N}$  and  $^{17}\text{O}$  in nitrosobenzene.

in recent approaches with explicit orthogonalization corrections.<sup>115,116</sup> Parameter optimization using either one of the three alternative expressions [eqs. (19), (34), (35)] led to essentially identical results for the goal function and the individual chemical shifts. The established MNDO expression, eq. (19), was therefore adopted in the final parameterization.

Gas phase chemical shifts of hydrogen atoms in OH and NH bonds experience large two-center diamagnetic contributions due to the heteroatom. This contribution may exceed 10 ppm for OH bonds, and is somewhat smaller for NH bonds. Reproducing these contributions requires Slater orbitals with exponents of about  $2.0 \text{ bohr}^{-1}$  on both N and O. Unfortunately, such small exponents (corresponding to diffuse orbitals) lead to a very poor description of the one-center terms on the heteroatoms themselves, and also to an unrealistically slow fall-off of the resonance integrals involving N and O. The parameterization cannot account for these deficiencies simultaneously, and we have therefore resorted to using separate  $\sigma_{\text{ref}}$  values for  $^1\text{H}$  in OH and NH bonds to mimic the two-center terms due to heteroatoms. Because the two-center diamagnetic terms fall off exponentially at typical bond distances, analogous problems are not encountered for longer bonds.

Separate  $\sigma_{\text{ref}}$  values for OH and NH result in a uniform adjustment to the three principal components of the  $^1\text{H}$  shielding tensor, whereas the underlying heteroatom contribution is strongly directional. Therefore, poor results may be expected for the individual tensor components of the  $^1\text{H}$  shielding tensor in OH and NH bonds. Because most of the shielding tensors are measured in condensed phase, where the  $^1\text{H}$  shielding in OH and NH groups is dominated by environmental effects, this shortcoming is unlikely to be important in practice.

Compared with standard MNDO, the present NMR-specific parameterizations primarily modify the resonance integrals  $H_{\mu\nu}$ , which mostly affect the paramagnetic contributions to the chemical shift by controlling the excitation energies, and thus the first-order density. The influence of the resonance integrals on the diamagnetic contributions is much less pronounced. Although large differences between dissimilar chemical environments are caused mostly by the paramagnetic terms,<sup>9</sup> the diamagnetic contributions may be important for the description of smaller substituent effects.

Therefore, it seems worthwhile to modify the one-center energies,  $U_{\mu\mu}$ , and the one-center two-electron integrals,  $g_{\mu\nu}$  and  $h_{\mu\nu}$ , in order to control the diamagnetic contributions and to tune the paramagnetic terms.<sup>58</sup> In corresponding parameterization attempts, the variation of  $g_{\mu\nu}$  and  $h_{\mu\nu}$  does not improve the quality of the computed chemical shifts, because changes in these integrals over a few electron volts are easily compensated by small adjustments in the one-center energies and resonance parameters. Therefore,  $g_{\mu\nu}$  and  $h_{\mu\nu}$  were fixed at their MNDO values.<sup>60,112</sup> Optimizing the one-center energies,  $U_{ss}$  and  $U_{pp}$ , on the other hand, has a profound effect on the one-center diamagnetic contributions to the shielding, which are proportional to the local atomic populations.<sup>39</sup> It turns out, however, that, in the absence of an absolute shielding reference, experimental chemical shifts alone do not sufficiently restrict the one-center energies on the more electronegative atoms (N, O) and that erratic changes in  $U_{ss}$  may occur in the course of such parameterizations. The inclusion of a suitable penalty function (see earlier) ensures that chemically reasonable  $U_{ss}$  values, atomic charges, and dipole moments are obtained without noticeably degrading the results for the chemical shifts.

The final parameter set includes 16 optimized parameters [ $U_{ss}(\text{H})$ ,  $\zeta(\text{H})$ ,  $\beta(\text{H})$ ,  $U_{ss}(\text{C})$ ,  $U_{pp}(\text{C})$ ,  $\zeta(\text{C})$ ,  $\beta_s(\text{C})$ ,  $\beta_p(\text{C})$ ,  $U_{ss}(\text{N})$ ,  $U_{pp}(\text{N})$ ,  $\zeta(\text{N})$ ,  $\beta(\text{N})$ ,  $U_{ss}(\text{O})$ ,  $U_{pp}(\text{O})$ ,  $\zeta(\text{O})$ , and  $\beta(\text{O})$ ], which are given in Table II. The six additional  $\sigma_{\text{ref}}$  parameters are fully determined by the optimized parameters and the reference set (Table III). These parameters are denoted as "method B" (no relation to the "method B" of ref. 58), or MB. Chemical shift calculations that include only one- and two-center terms are designated MB2, whereas full calculations with three-center terms are labeled MB3. An analogous notation applies to method A (i.e., MA2 and MA3).

Comparison of the MA and MB parameters in Table II shows that the optimized parameters can exhibit significant variations while still providing a reasonable description of the isotropic shielding. Thus, all MA orbital exponents are significantly smaller than in MNDO, whereas the MB orbital exponents are somewhat larger than in MNDO. In both cases, however, the resonance integrals  $H_{\mu\nu}$  are larger than in MNDO, and are comparable over the range of typical bond lengths.

Overall, the optimized MB parameters appear to be physically reasonable, with one potential exception. The  $U_{ss}$  and  $U_{pp}$  values of oxygen are



probably too low, thus exaggerating the negative charge on oxygen atoms and the corresponding one-center diamagnetic contributions. Because oxygen is the most electronegative element in the present parameterization, this imbalance does not adversely affect the relative shieldings for compounds containing H, C, N, and O.

## Results and Discussion

### GENERAL

NMR chemical shifts are obtained as the difference between a reference shielding,  $\sigma_{\text{ref}}$ , and the calculated absolute isotropic shielding,  $\sigma$  [see eqs. (1)–(3) and (23)–(28)]. In our approach, the reference shielding is optimized such that the mean deviation between theoretical and experimental chemical shifts vanishes for the chosen reference set. The  $\sigma_{\text{ref}}$  values will therefore depend not only

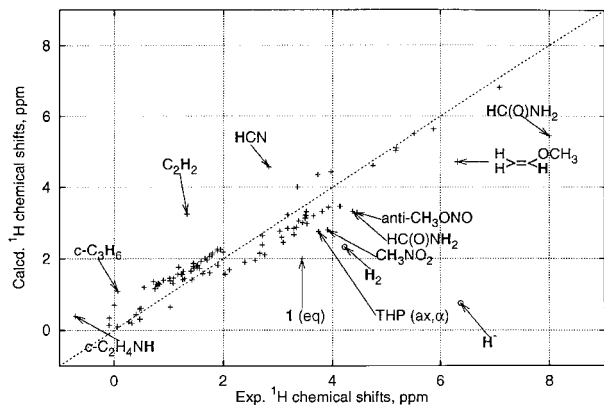
on the corresponding experimental standard, but also on the choice of reference modules and the computational protocol (e.g., geometries and integral approximations). They will absorb any systematic errors of the calculated absolute shieldings, in an average sense (e.g., missing contributions from core electrons).

Table III lists the NMR chemical shifts for the molecules from the small reference set that have been computed at the MA3 and MB3 levels using the parameters from Table II and optimized B3-LYP/6-311G\*\* geometries. The corresponding statistical evaluations are shown in Table IV. For the sake of comparison, Table IV also contains the statistical results for full chemical shift calculations with the original MNDO parameters (M3) and for calculations without three-center terms (M2, MA2, and MB2). Correlations between the experimental and theoretical (MB3) chemical shifts are shown in Figures 1–4.

**TABLE IV.**  
Results for Small Reference Set at B3LYP Geometries.<sup>a</sup>

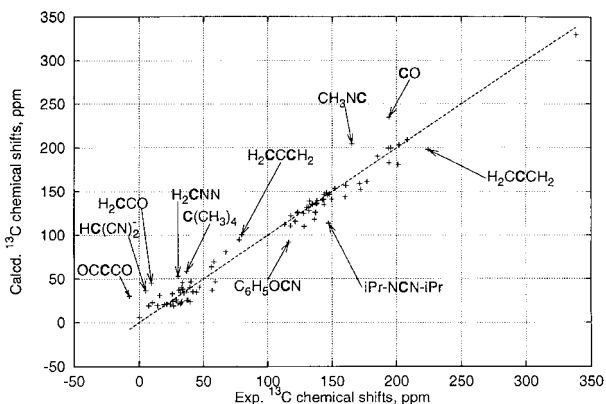
Element		MNDO		Method A		Method B	
		M2 <sup>b</sup>	M3 <sup>c</sup>	MA2 <sup>b</sup>	MA3 <sup>c</sup>	MB2 <sup>b</sup>	MB3 <sup>c</sup>
H (102 values)	$\sigma_{\text{ref}}$ (ppm)	48.854	51.717	48.863	51.918	48.051	50.064
	$\sigma_{\text{ref}}$ (N—H) (ppm)	42.556	44.186	45.684	46.415	43.037	42.873
	$\sigma_{\text{ref}}$ (O—H) (ppm)	41.335	41.438	47.009	46.287	38.795	37.897
	RMS error (ppm)	1.050	1.052	0.686	0.691	0.848	0.611
	Mean abs. error (ppm)	0.803	0.706	0.566	0.497	0.656	0.457
	Maximum error (ppm)	2.956	3.426	2.446	1.983	3.477	2.558
	Ordering (max. 29) <sup>d</sup>	17	22	20	23	24	25
C (93 values)	$\sigma_{\text{ref}}$ (ppm)	−114.17	−111.14	49.70	52.11	68.51	69.53
	RMS error (ppm)	41.48	40.97	20.13	20.53	13.70	13.57
	Mean abs. error (ppm)	29.61	29.34	11.78	12.12	9.79	9.65
	Maximum error (ppm)	173.97	176.04	116.79	119.20	39.87	40.88
	Ordering (max 29) <sup>d</sup>	15	16	26	26	24	25
N (37 values)	$\sigma_{\text{ref}}$ (ppm)	−553.02	−552.48	−241.24	−241.04	−172.61	−172.20
	RMS error (ppm)	169.01	169.33	61.70	61.22	39.46	39.55
	Mean abs. error (ppm)	110.90	111.06	51.13	50.51	33.53	33.70
	Maximum error (ppm)	665.45	668.36	153.88	155.47	104.14	104.47
	Ordering (max 6) <sup>d</sup>	4	4	4	4	4	4
O (51 values)	$\sigma_{\text{ref}}$ (ppm)	−426.55	−426.00	75.29	75.97	281.08	281.57
	RMS error (ppm)	277.42	278.56	88.42	88.17	80.48	80.55
	Mean abs. error (ppm)	199.27	200.48	64.30	63.70	59.90	59.75
	Maximum error (ppm)	1261.41	1265.05	304.26	307.73	242.71	244.95
	Ordering (max 8)	7	7	8	8	7	7

<sup>a</sup> Some of the chemical shift values in Table III are excluded from the statistics (see text). <sup>b</sup> Including one- and two-center terms only. <sup>c</sup> Including one-, two-, and three-center terms. <sup>d</sup> For molecules with more than one magnetically inequivalent nucleus of the same element; number of molecules where the relative order of the chemical shifts is reproduced correctly.

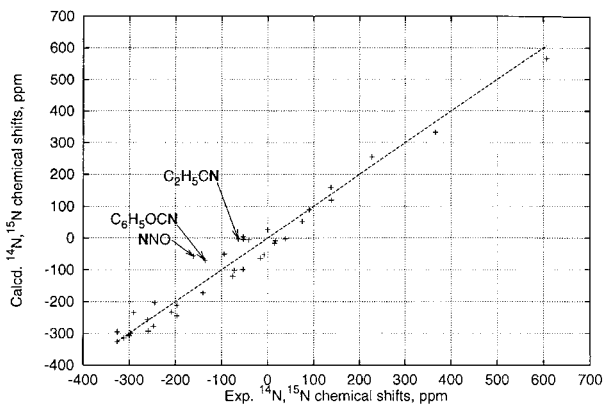


**FIGURE 1.** Correlation between experimental and calculated (MB3//B3LYP)  $^1\text{H}$  chemical shifts. Experimental values for hydrogen-bonded hydrogens and  $\text{H}^+$  are in excess of 9 ppm, and are not shown. Values excluded from statistics are represented by the open circles. Arrows indicate values with deviations from experiment exceeding  $0.917\text{ ppm}$  ( $1.5\sigma$ ). THP is tetrahydropyran; 1 is trimethylhexahydrotriazine. Chemical shifts are given relative to gaseous methane.

The use of accurate B3LYP structures for the small reference set (Tables III and IV) minimizes errors arising from inadequate geometries. Semiempirical NMR computations for large molecules will generally not afford such a sophisticated and expensive method for geometry optimization, but will normally rely on semiempirical structures. Table V therefore presents optimum  $\sigma_{\text{ref}}$  values for MA2, MA3, MB2, and MB3 in combination with optimized MNDO, AM1, and PM3 geometries, respectively, along with the corresponding



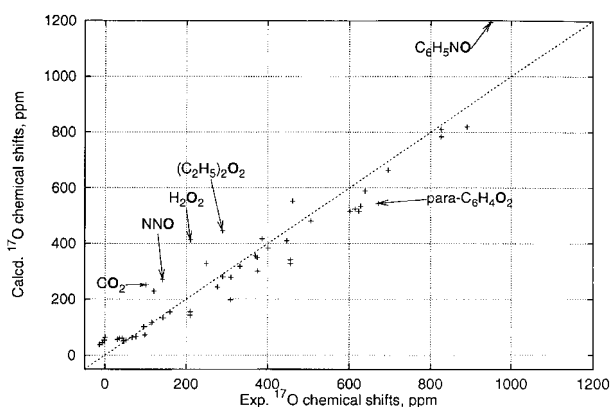
**FIGURE 2.** Correlation between experimental and calculated (MB3//B3-LYP)  $^{13}\text{C}$  chemical shifts. Arrows indicate values with deviations from experiment exceeding  $20.4\text{ ppm}$  ( $1.5\sigma$ ). Chemical shifts are given relative to gaseous methane.



**FIGURE 3.** Correlation between experimental and calculated (MB3//B3-LYP)  $^{14}\text{N}$ ,  $^{15}\text{N}$  chemical shifts. Arrows indicate values with deviations from experiment exceeding  $59.3\text{ ppm}$  ( $1.5\sigma$ ). Chemical shifts are given relative to gaseous nitrogen.

RMS errors. It should be emphasized that the results in Table V refer to single-point NMR calculations at standard MNDO, AM1, and PM3 geometries, because the NMR-specific parameters (Table II) do not provide realistic geometries.

The majority of the experimental NMR chemical shifts in the small reference set come from gas phase data (Table III). On the other hand, routine NMR work is usually performed in solution. It is therefore also desirable to convert the computed absolute shieldings to liquid phase chemical shifts that refer to the accepted liquid phase standards. The required  $\sigma_{\text{ref}}$  values for the MA2, MA3, MB2, and MB3 methods in combination with semiempir-



**FIGURE 4.** Correlation between experimental and calculated (MB3//B3-LYP)  $^{17}\text{O}$  chemical shifts. Experimental values for ozone are in excess of 1200 ppm, and are not shown. Arrows indicate values with deviations from experiment exceeding  $120\text{ ppm}$  ( $1.5\sigma$ ). Chemical shifts are given relative to gaseous water.

**TABLE V.**  
**Influence of Molecular Geometry and Three-Center Terms on Computed Chemical Shifts<sup>a</sup> (Small Set).**

Method and geometry		$\sigma_{\text{ref}}$ (ppm)						RMS error (ppm)				
		H	H(N)	H(O)	C	N	O	H	C	N	O	(O) <sup>b</sup>
MA2	B3LYP <sup>c</sup>	48.863	45.684	47.009	49.70	-241.24	75.29	0.686	20.13	61.70	88.42	(89.93)
	MNDO <sup>d</sup>	48.006	46.118	48.146	46.20	-238.97	77.07	0.770	20.60	67.86	92.91	(93.85)
	AM1	47.713	46.511	47.087	47.32	-235.69	74.39	0.820	21.17	68.99	92.82	(94.09)
	PM3	48.471	46.629	48.222	48.92	-245.48	67.88	0.720	20.24	63.36	92.99	(94.47)
MA3	B3LYP <sup>c</sup>	51.918	46.415	46.287	52.11	-241.04	75.97	0.691	20.53	61.22	88.17	(89.68)
	MNDO <sup>c</sup>	50.966	46.867	47.240	48.47	-238.83	77.62	0.503	20.99	67.38	92.81	(93.73)
	AM1	50.605	47.248	46.321	49.64	-235.56	75.01	0.554	21.69	68.43	92.61	(93.87)
	PM3	51.508	47.399	47.391	51.32	-245.29	68.56	0.735	20.76	62.77	92.87	(94.36)
MB2	B3LYP <sup>c</sup>	48.051	43.037	38.795	68.51	-172.61	281.08	0.848	13.70	39.46	80.48	(73.50)
	MNDO <sup>d</sup>	47.248	43.409	39.791	64.81	-169.21	284.28	0.941	13.43	47.11	78.41	(79.65)
	AM1	46.947	43.845	38.727	66.08	-166.35	286.53	0.969	13.20	47.44	76.91	(78.03)
	PM3	47.680	43.990	39.721	67.89	-175.21	270.23	0.856	12.94	43.40	99.20	(82.66)
MB3	B3LYP <sup>c</sup>	50.064	42.873	37.897	69.53	-172.20	281.57	0.611	13.57	39.55	80.55	(73.55)
	MNDO <sup>c</sup>	49.170	43.266	38.827	65.75	-168.83	284.72	0.567	13.30	47.17	78.51	(79.75)
	AM1	48.835	43.663	37.813	67.04	-165.97	286.98	0.627	13.20	47.48	76.97	(78.09)
	PM3	49.669	43.853	38.775	68.90	-174.82	270.72	0.627	12.90	43.50	99.32	(82.79)

<sup>a</sup> NMR chemical shifts relative to gaseous reference compounds: CH<sub>4</sub> for <sup>13</sup>C and <sup>1</sup>H; N<sub>2</sub> for <sup>14</sup>N and <sup>15</sup>N; H<sub>2</sub>O for <sup>17</sup>O. <sup>b</sup> Excluding peroxides (two chemical shifts). <sup>c</sup> Using 6-311G\*\* basis set. <sup>d</sup> Constrained geometries used for some molecules (see text).

ical geometries are given in Table VI for the large reference set that is based on liquid phase data (see earlier). The corresponding RMS errors are also provided. A detailed analysis of the results for the large set will be given elsewhere.<sup>97</sup> The remainder of this section focuses on the gas phase results for the small reference set (Tables III–V).

## HYDROGEN

As can be seen from Table IV, the three-center terms are essential for the description of hydrogen chemical shifts. On average, the three-center terms contribute about 2 ppm to the absolute <sup>1</sup>H shielding in MB, and reduce the overall RMS error by

**TABLE VI.**  
**Influence of Molecular Geometry and Three-Center Terms on Computed Chemical Shifts<sup>a</sup> (Large Set).**

Method and geometry		$\sigma_{\text{ref}}$ (ppm)						RMS error (ppm)				
		H	H(N)	H(O)	C	N	O	H	C	N	O	(O) <sup>b</sup>
MA2	MNDO <sup>c</sup>	48.942	48.828	50.090	41.50	-299.15	30.16	1.235	13.66	53.17	62.87	(62.11)
	AM1	48.638	48.898	49.120	43.12	-298.66	27.81	1.189	13.58	53.26	62.09	(61.81)
	PM3	49.145	49.101	49.525	44.45	-306.87	23.68	1.072	13.35	51.70	68.44	(63.84)
MA3	MNDO <sup>c</sup>	50.629	49.300	49.892	43.95	-298.60	30.14	0.913	13.66	52.74	62.82	(62.02)
	AM1	50.298	49.324	48.882	45.63	-298.12	27.86	0.779	13.71	52.79	61.83	(61.51)
	PM3	50.893	49.579	49.493	47.04	-306.30	23.79	1.079	13.42	51.23	68.17	(63.61)
MB2	MNDO <sup>c</sup>	49.012	46.431	43.094	58.02	-232.20	256.83	1.845	11.87	37.22	57.47	(57.63)
	AM1	48.679	46.636	42.064	59.60	-232.52	260.90	1.789	11.55	36.29	58.87	(58.76)
	PM3	49.174	46.818	42.383	61.13	-241.07	242.96	1.601	11.72	37.79	98.36	(62.86)
MB3	MNDO <sup>c</sup>	49.900	45.994	42.423	59.09	-231.72	256.97	1.076	11.66	37.26	57.23	(57.38)
	AM1	49.544	46.107	41.395	60.70	-232.05	261.02	1.009	11.46	36.33	58.51	(58.39)
	PM3	50.099	46.361	41.741	62.28	-240.58	243.13	0.952	11.60	37.85	98.15	(62.58)

<sup>a</sup> NMR chemical shifts relative to liquid reference compounds: TMS for <sup>13</sup>C and <sup>1</sup>H; nitromethane for <sup>14</sup>N and <sup>15</sup>N; water for <sup>17</sup>O.

<sup>b</sup> Excluding peroxides (six chemical shifts). <sup>c</sup> Constrained geometries used for some molecules (see text).

more than 25%, from 0.85 ppm to 0.61 ppm. This final RMS error is comparable to the typical vibrational corrections to  $^1\text{H}$  shielding ( $\geq 0.3$  ppm<sup>32,33</sup>), which are apparently taken into account to some extent by the semiempirical parameters.

Five  $^1\text{H}$  chemical shifts in Table III are excluded from the final statistical estimates.  $\text{H}^+$ ,  $\text{H}^-$ , and  $\text{H}_2$  are considered to be untypical for semiempirical applications. The errors for these systems are largely due to orthogonalization effects (see later), which are neglected in MNDO. The other two excluded shifts belong to protons in strong intramolecular hydrogen bonds that occur in the enol form of acetylacetone and one of its derivatives. These extremely deshielded shifts are due to a combination of several factors,<sup>117</sup> which are not described in a balanced manner by MB. The most important contribution due to the paramagnetic currents in the H bond is reasonably well reproduced in MB, but the reduction in the exponentially decaying two-center shielding due to the oxygen atoms is overestimated, and the exceptionally large vibrational contribution arising from the flat potential energy surface is not covered explicitly. The constant offset term used to mimic the two-center contribution in MB is not flexible enough to capture these effects (see earlier). MA, with its more diffuse atomic orbitals on O and N, reproduces these  $^1\text{H}$  shifts somewhat better.

Other outliers in the  $^1\text{H}$  correlation plot (see Fig. 1) include hydrogens in three-membered ring compounds, which are too deshielded by about 1 ppm, possibly due to the insufficient flexibility of the single- $\zeta$  valence basis set. There are rather large errors in  $\text{C}_2\text{H}_2$  and HCN, where the hydrogens are too shielded by about 2 ppm. In molecules containing electronegative substituents,  $\alpha$  hydrogens are typically too shielded by 0.5 to 1.5 ppm. For some of the outliers in Figure 1, unusually large vibrational and conformational averaging effects (methylnitrite, trimethylhexahydrotriazine) and association effects (formamide) may also contribute. Hydrogen shifts in hydrocarbons are typically overestimated by about 0.3 ppm. If the fit is restricted to hydrocarbons alone (24 individual shifts), the RMS error is reduced by almost 30% to 0.423 ppm, and only one molecule ( $\text{C}_2\text{H}_2$ ) has an error exceeding 0.7 ppm.

As can be inferred from Table V, absolute  $^1\text{H}$  shieldings are strongly influenced by the molecular geometry. The difference between the MB3  $\sigma_{\text{ref}}$  values for AM1 and B3LYP geometries (1.3 ppm) exceeds the corresponding RMS errors in the

chemical shifts (0.63 and 0.61 ppm, respectively). It is therefore extremely important to use systematically obtained geometries when computing hydrogen chemical shifts. Although the RMS errors in the  $^1\text{H}$  chemical shifts are increased for the liquid phase chemical shifts, the overall agreement is still fair (see Table VI).

## CARBON

The correlation plot for the MB3  $^{13}\text{C}$  results is shown in Figure 2. A large fraction of the overall RMS error of 13.6 ppm is due to small molecules with unusual bonding situations ( $\text{CO}$ ,  $\text{C}_3\text{O}_2$ , diazomethane, ketene, allene, methylisonitrile). For hydrocarbons (46 chemical shifts), the RMS error amounts to 9.3 ppm. Ions are well described on average (15.4 ppm, 8 shifts). Much larger errors are found for molecules with cumulated double bonds (23.0 ppm, 13 shifts). The experimental chemical shifts for the central carbon atoms in allene and carbon suboxide differ by 231.9 ppm (MB3: 168.1 ppm), or more than half of the total experimental range for  $^{13}\text{C}$ , despite the formally identical local chemical environment, which indicates an extremely flexible electronic structure in these molecules. The single- $\zeta$  Slater basis employed in MNDO may not be flexible enough to describe the underlying redistribution of the electron density.

It is of interest to note that some of the molecules with the largest residual errors in MB3 also present difficulties for noncorrelated *ab initio* approaches. Thus, the near basis set limit RHF-GIAO  $^{13}\text{C}$  results for CO and for the middle carbon atom in allene deviate from experiment by 28 ppm<sup>18</sup> and 16 ppm,<sup>36</sup> respectively. The corresponding MB3 errors are 41 and 26 ppm.

The relatively large MB3 error for the cyano carbon in phenylcyanate (24 ppm) is somewhat surprising, given that MB3 reproduces the shielding in cyano groups fairly well (HCN: less than 1-ppm error; acetonitrile: 5.5-ppm error; malonodinitrile: 7-ppm error). In this case, part of the error may be due to association effects in the neat phenylcyanate used in the experimental measurements.<sup>118</sup>

Although MB3 reproduces variations in the chemical shifts of  $sp^2$  carbons fairly well (110 to 220 ppm relative to methane; see Fig. 2), the smaller effects of substitution at  $sp^3$  carbons are not described accurately. The MB3  $^{13}\text{C}$  chemical shifts in alkanes are primarily determined by the nearest-

neighbor atoms. The MB3 shift for methane is 6 ppm, whereas primary, secondary, tertiary, and quaternary carbon atoms cluster around 20, 33, 45, and 58 ppm, respectively. Even though the experimental  $^{13}\text{C}$  shifts in hydrocarbons tend to be higher for more crowded atoms, the variation of the shifts is much larger experimentally than found in MB3. Thus, in the small reference set, the chemical shifts for the primary, secondary, and tertiary carbon atoms in aliphatic hydrocarbons (excluding cyclopropane) cover ranges of 25, 19, and 7 ppm, respectively, compared with just 5, 5, and 1 ppm in MB3. This deficiency is evident in the horizontal "striping" of the correlation plot in Figure 2 in the 0- to 50-ppm region. The same problem is shared by the MA3 approach,<sup>58</sup> which indicates an underlying physical reason rather than a deficiency in the semiempirical parameterization.

Three-center terms contribute about 1 ppm to  $^{13}\text{C}$  absolute shielding, on average, and can be ignored in most cases without significantly degrading the results (small set RMS: 13.70 ppm for MB2 and 13.57 ppm for MB3). Exceptions are molecules with extensively conjugated systems, cumulated double bonds, or crowded substituents, where three-center terms may contribute several ppm toward the chemical shift. The largest three-center contribution to the  $^{13}\text{C}$  shift in the small set is 4.1 ppm (ring junction carbon atoms in azulene).

As can be seen from Tables V and VI, optimized MNDO, AM1, and PM3 geometries are generally satisfactory for the evaluation of chemical shifts and yield essentially identical RMS errors for both reference sets. When comparing results for different molecules, it is of course advisable to use geometries from the same semiempirical method. It should also be kept in mind, however, that apparent MB3 failures (e.g., in homoaromatic and nonclassical ions<sup>97</sup>) can sometimes be traced to qualitatively incorrect semiempirical geometries. As a rule of thumb, reasonable results may be expected only if errors in interatomic distances do not exceed 0.05 Å.

## NITROGEN AND OXYGEN

The correlation between the experimental and calculated nitrogen chemical shifts for the small set is shown in Figure 3. The largest error (105 ppm) is observed for the terminal nitrogen atom in nitrous oxide. It is also hard to predict this shift by *ab initio* approaches; with large basis sets, the

RHF-GIAO result deviates from experiment by 46 ppm, whereas MP2 is off by 24 ppm.<sup>36</sup> Surprisingly, other molecules that are difficult for *ab initio* and DFT calculations, including  $\text{N}_2$ <sup>18</sup> and various nitroso compounds,<sup>37</sup> are described fairly well by MB3.

Due to the increased range of chemical shifts, three-center terms are even less important for nitrogen than for carbon, and can usually be ignored. Using geometries from different semiempirical methods may, however, cause systematic differences in chemical shifts of up to 10 ppm (see Tables V and VI). Although semiempirical geometries are generally acceptable for the evaluation of the nitrogen chemical shifts (see RMS errors in Tables V and VI), certain classes of N—O and N—N bond lengths are not well reproduced by these methods.<sup>60,110,111</sup> Thus, the MB3 chemical shifts for the nitroso nitrogen in  $\text{N}_2\text{O}_3$  vary over more than 40 ppm, depending on the particular choice of semiempirical geometry (MNDO: 325 ppm; AM1: 311 ppm; PM3: 353 ppm, compared to B3LYP: 333 ppm). As for  $^{13}\text{C}$ , bond lengths must normally be accurate to better than 0.05 Å for qualitatively correct results.

The correlation plot for  $^{17}\text{O}$  chemical shifts is given in Figure 4. The RMS errors for the small reference set are lowered by only 9% in MB3 relative to MA3 (80.6 ppm vs. 88.2 ppm), compared with an improvement of about 35% for C and N. This may be caused in part by some scatter in the experimental reference data; difficulties in obtaining  $^{17}\text{O}$  NMR spectra<sup>108,109</sup> often necessitate measurements on neat liquids and concentrated solutions. The resulting chemical shifts may be influenced by association and environmental effects, which may be sizeable due to the exposed nature of the oxygen lone pairs, the large dipole moments, and the easily polarizable double bonds in oxygen compounds. An adequate description of the oxygen chemical shifts is also known to require large basis sets at the *ab initio* level,<sup>9</sup> so that the insufficient flexibility of the single- $\zeta$  valence basis set in MNDO may also play a role.

The largest deviation of the MB3 oxygen chemical shifts from experiment is found for nitrosobenzene (1194 vs. 949 ppm relative to gaseous water). The corresponding deviation is even larger for the *ab initio* and DFT results (RHF-IGLO: 2212 ppm; UDFT-IGLO: 1926 ppm; SOS-DFPT-IGLO: 1532 ppm).<sup>36</sup> The oxygen chemical shifts in other nitroso compounds are described relatively well by MB3 (over a wide range, see Table III), and the

nitrogen chemical shift in  $C_6H_5NO$  is also well reproduced. It is known experimentally that the nitrogen shielding in nitrosobenzene depends strongly on the equilibrium of the dimerization reaction, so that the apparent chemical shift may vary over 500 ppm depending on the solvent.<sup>119</sup> A comparable dependence may be expected for  $^{17}O$  shifts. Because the only experimental value for the oxygen chemical shift of nitrosobenzene<sup>120</sup> has not been examined for solvent dependence and is reported in an ambiguous manner (with an apparent interchange of the nitrogen and oxygen shifts), an experimental reinvestigation is strongly indicated.

Other problem cases for oxygen chemical shifts in MB3 include small linear molecules with cumulated double bonds ( $CO_2, N_2O$ ), which are too deshielded by about 150 ppm. Chemical shifts of peroxidic oxygens are overestimated by about 180 ppm, whereas the carbonyl oxygens in aldehydes and ketones are systematically too shielded by ca. 100 ppm. The latter error may be partly due to very large solvent effects on the carbonyl  $^{17}O$  chemical shifts.<sup>121</sup> In ozone, the chemical shifts of both the middle and terminal oxygens are overestimated by about 400 ppm in MB3. These large deviations are not surprising, because the ozone chemical shifts can be described at the *ab initio* level only when using a sophisticated treatment of electron correlation.<sup>19,122</sup> The statistical evaluations for  $^{17}O$  chemical shifts in Tables IV to VI exclude ozone, because it is not representative for semiempirical applications.

As for nitrogen, three-center terms do not contribute significantly to the oxygen chemical shifts, whereas using consistent geometries may be important for meaningful comparisons (see Tables V and VI). Semiempirical geometries are usually adequate with the exception of molecules containing N—O and O—O bonds. Oxygen chemical shifts in peroxides provide an illustration of the importance of the chosen geometries. The relatively large residual error for  $^{17}O$  chemical shifts computed at PM3 geometries (small[large] set: 99.3[98.2] vs. 78.5[57.2] ppm for MNDO) is dominated by peroxides (two and six shifts in the small and large sets, respectively). PM3 grossly overestimates the O—O bond lengths,<sup>111</sup> thus increasing the already too deshielded  $^{17}O$  shifts in these compounds. MNDO and AM1, on the other hand, strongly underestimate O—O distances in peroxides,<sup>60,110</sup> and thereby decrease the chemical shifts and the overall RMS errors. Once the problematic molecules are removed from the reference set, geometries

from all three semiempirical methods produce results of comparable quality (see Tables V and VI).

## OVERLAP EFFECTS

Relative to the experimentally accessible range, the MB3 errors in the chemical shifts of  $H^+$ ,  $H^-$ , and  $H_2$  are by far the largest in the small reference set (Table III). It is instructive to analyze the underlying reasons for this failure, which cannot be removed by semiempirical parameterization without abandoning some of the approximations made in the MNDO model.

In a minimal valence basis set, the wave function of  $H_2$  is completely determined by symmetry, so that all terms containing the first-order density matrix vanish in eqs. (23)–(28). The zero-order density matrix in MNDO approximation is given by:

$$\mathbf{P}^{\text{MNDO}} = \begin{pmatrix} 1 & 1 \\ 1 & 1 \end{pmatrix} \quad (36)$$

The MNDO isotropic shielding in  $H_2$  is therefore:

$$\sigma_{\text{iso}}^{\text{MNDO}} = \frac{1}{3c^2} \left\{ \zeta + \frac{1}{r} (1 - e^{-2\zeta r}) - \zeta e^{-2\zeta r} - r\zeta^2 f(2\zeta r) + 2\zeta(1 + \zeta r)e^{-\zeta r} \right\} \quad (37)$$

where the function  $f(x)$  is defined by:

$$f(x) = \int_{-1}^1 dt \int_0^\infty du \{ te^{-\sqrt{u^2+x^2-2xut}} \} \quad (38)$$

In *ab initio* Hartree-Fock calculations with a minimal basis set, the approximation of zero-diatomic overlap<sup>60</sup> is not invoked, and the density matrix is given by:

$$\mathbf{P} = \frac{1}{1+S} \mathbf{P}^{\text{MNDO}} \quad (39)$$

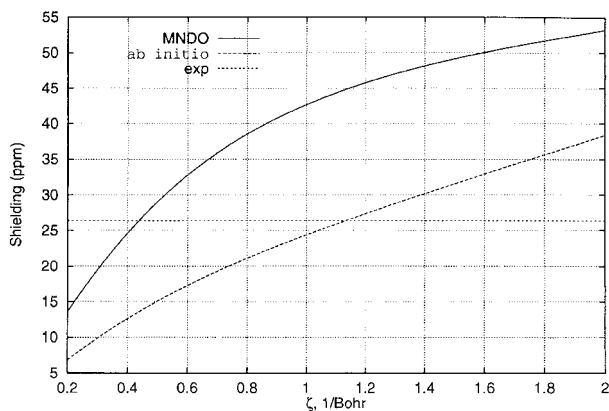
where the overlap integral  $S$  is obtained from:

$$S = \frac{1}{3} e^{-\zeta r} (3 + 3\zeta r + \zeta^2 r^2) \quad (40)$$

The *ab initio* isotropic shielding then becomes:

$$\sigma_{\text{iso}} = \frac{1}{1+S} \sigma_{\text{iso}}^{\text{MNDO}} \quad (41)$$

As can be seen from Figure 5, the absolute shielding in  $H_2$  at the experimental equilibrium geometry (or, equivalently, the difference of the chemical shifts in  $H_2$  and  $H^+$ ) can be reproduced



**FIGURE 5.** Dependence of the absolute isotropic shielding in  $\text{H}_2$  on the orbital exponent of the minimal Slater valence basis set, at the experimental equilibrium geometry.

by the *ab initio* expression [eq. (41)] with a physically reasonable value of about  $1.1 \text{ bohr}^{-1}$  for the orbital exponent  $\zeta$ . The overlap-free MNDO expression [eq. (37)], on the other hand, cannot reproduce the experimental shielding for any sensible choice of  $\zeta$  and  $r_{\text{HH}}$ . Further examination of eqs. (37) and (41) shows that the *ab initio* expression goes to the limit of  $2\zeta/3c^2$  at  $r_{\text{HH}} = 0$ , which is the correct minimal basis set result for isotropic shielding in  $\text{H}^-$ . The corresponding limit of the MNDO expression is  $4\zeta/3c^2$ , twice the (correct) MNDO result for  $\text{H}^-$ . It is therefore impossible to describe the absolute shielding in  $\text{H}^-$  and  $\text{H}_2$  at the same time without abandoning the ZDO (zero differential overlap) approximation or using an explicitly orthogonalized basis set for the matrix elements in eqs. (26)–(28). It should be noted, of course, that such overlap effects are especially pronounced in  $\text{H}_2$  and that they can often be absorbed in less demanding cases by the semiempirical parameterization, at least in an average sense.

## Conclusion and Outlook

The evaluation of the NMR chemical shift tensor has been implemented at the semiempirical MNDO/d level using GIAOs and analytic derivative theory. NMR-specific parameters are required for the qualitatively correct description of the experimental chemical shifts. Optimization of the orbital exponents, resonance  $\beta$  parameters, and one-center energies of H, C, N, and O (for the total of 16 parameters) leads to residual RMS errors of

less than 5% of the experimental chemical shift range for each of the four elements. A significant fraction of the error is due to a few small molecules with unusual bonding situations, which are also challenging in *ab initio* calculations. The overall quality of the results is usually competitive with low-level *ab initio* and DFT calculations at a fraction of the cost.

Three-center terms are required for the qualitatively correct description of the  $^1\text{H}$  shielding, and may be important for some  $^{13}\text{C}$  chemical shifts in the presence of aromatic systems, crowded substituents, and cumulated double bonds. These terms are not significant for nitrogen and oxygen shielding, and may be discarded for carbon in most cases. Omitting the three-center contributions reduces computation times typically by more than an order of magnitude.

Semiempirical geometries from MNDO, AM1, and PM3 are generally adequate for the calculation of isotropic chemical shifts, provided that consistent geometries are used for all molecules. Exceptions are molecules containing N—O and O—O bonds and, for MNDO, also some systems in which conjugation determines the relative orientation of the substituents.

Insufficient flexibility of the single- $\zeta$  Slater set used in MNDO prevents quantitative description of the shielding for hydrogen-bonded protons, even though the qualitative trends are reproduced correctly. Model-inherent problems occur in the hydrogen molecule and possibly also in other systems in which variations of the diamagnetic contribution due to changes in overlap are significant. This deficiency cannot be removed by parameterization alone, and requires an improvement of the underlying ZDO approximation.

Due to its relatively low computational cost and its reasonable accuracy, the present method can be used to study NMR chemical shifts and their trends in large systems, as well as the effects of molecular dynamics on the chemical shift. It should also allow for the rapid screening of compounds of industrial interest, because routine calculations on molecules with several hundred atoms are possible.

Future developments of the method may include an explicit account of orthogonalization effects that may provide a better description of hydrogen chemical shifts and of diamagnetic terms in general. Incorporation of spin-orbit effects may be necessary for the treatment of the shielding in halogens<sup>123</sup> and other heavier elements.<sup>124</sup> Finally,

extending the existing program to handle NMR coupling constants is also desirable.

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